Long-term antipsychotic polypharmacy prescribing in secondary mental health care: detection, predictors and outcomes.

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Long-term antipsychotic polypharmacy prescribing in secondary mental health care: detection, predictors and outcomes.

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ABSTRACT

Background: Investigating long-term antipsychotic polypharmacy is key to unpacking the associations between serious mental illnesses (SMI) and detrimental outcomes, such as premature death and frequent hospital readmissions, observed in this population. However, existing research is sparse and hampered by methodological problems such as examining small and homogeneous samples and residual confounding.

Objectives:

1) To identify cases on long-term antipsychotic polypharmacy (≥ 6 months) prescribing in South London and Maudsley electronic health records (EHR);
2) To identify factors that predict long-term antipsychotic polypharmacy prescribing for SMI patients in secondary mental health care;
3) To investigate whether outcomes such as hospital readmission and mortality are associated with long-term antipsychotic polypharmacy prescribing in secondary mental health care.

Methods: Antipsychotic medication information was derived from the Clinical Record Interactive Search (CRIS), a de-identified electronic patient records system, for the period between 2007 and 2014. Data on mortality were extracted using existing linkages between CRIS and death certification (Office of National Statistics). Information about antipsychotic co-prescribing was extracted using a bespoke algorithm. Multivariable logistic models were built to investigate predictors of antipsychotic polypharmacy. To investigate the impact of antipsychotic polypharmacy on hospital readmission and all-cause

mortality, I constructed multivariable Cox proportion hazard models. To test the association between long-term antipsychotic polypharmacy and cause-specific mortality I used competing risk regression.

Implications: On a clinical level, this thesis provides an insight into factors that can predict clinical decision-making regarding antipsychotic polypharmacy prescribing in real-life clinical settings. On a patient level, the findings highlight patient burden associated with this antipsychotic regimen. In the wider treatment, service and policy context, the lack of patient benefit from antipsychotic polypharmacy highlights the need for programmes that target prescribers, to reduce antipsychotic polypharmacy.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
BNF	British National Formulary
BPRS	Brief Psychiatric Rating Scale
BRC	Biomedical Research Centre
CGI	Clinical Global Impressions Scale
CRIS	Clinical Record Interactive Search
CTOs	Community Treatment Orders
EHR	Electronic Health Records
FGA	First Generation Antipsychotic
GAF	Global Assessment of Functioning
GATE	General Architecture for Text Engineering
HoNOS	Health of the Nation Outcome Scale
HR	Hazard Ratio
ICD	International Classification of Diseases
LAI	Long-acting Injectable
NHS	National Health Service
NLP	Natural Language Processing
ONS	Office of National Statistics
OR	Odds ratio
PANSS	Positive and Negative Syndrome Scale
PJS	Patient Journey System
PRN	pro re nata
PTSD	Post Traumatic Stress Disorder
QTc	Quantum Tunnelling Corrected
SGA	Second Generation Antipsychotic
SLAM	South London and Maudsley
SMI	Serious Mental Illnesses
SOFAS	Social and Occupational Functioning Assessment Scale
SQL	Structured Query Language

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Publications in peer-reviewed journals

Kadra, G., Stewart, R., Shetty, H., Jackson, R. G., Greenwood, M. A., Roberts, A., Chang, C.-K., MacCabe, J. H., and Hayes, R. D. (2015). Extracting antipsychotic polypharmacy data from electronic health records: developing and evaluating a novel process. *BMC Psychiatry*, *15*(1), 166. doi:10.1186/s12888-015-0557-z

Perera, G., Broadbent, M., Callard, F., Chang, C.-K., Downs, J., Dutta, R., Fernanades, A., Hayes, RD., Henderson, M., Jackson, R., Jewell, A., **Kadra, G**., Little, R., Pritchard, M., Shetty, H., Tulloch, A. & Stewart, R. (2016). Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. *BMJ Open* , *6* (3). doi:10.1136/bmjopen-2015-008721

Kadra, G., Stewart, R., Shetty, H., Downs, J., MacCabe, J. H., Taylor, D., & Hayes, R. D. (2016). Predictors of long-term (≥ 6months) antipsychotic polypharmacy prescribing in secondary mental health care. Schizophrenia Research, 174, 1-3.

Presentations at international conferences

Oral Presentation, 18th EPA Section Epidemiology and Social Psychiatry, Gothenburg, Sweden: *"Long-term antipsychotic polypharmacy prescribing and mortality".*

Oral Presentation, 15th International Congress of the International Federation of Psychiatric Epidemiology, Bergen, Norway: "*Predictors of long-term antipsychotic polypharmacy prescribing in clinical settings".*

Oral Presentation, 11th International Conference of the European Network for Mental Health Service Evaluation, Malaga, Spain: *"Predictors of long-term antipsychotic polypharmacy prescribing in clinical settings".*

Oral Presentation, 17th EPA Section Epidemiology and Social Psychiatry, Ulm, Germany: *"Evaluating a new natural language processing application for extracting antipsychotic medication data from clinical records".*

CHAPTER OUTLINE

CHAPTER 1: Provides a broad introduction and background to antipsychotic polypharmacy prescribing in mental health settings.

CHAPTER 2: Provides a literature review of predictors and outcomes associated with long-term antipsychotic polypharmacy prescribing for individuals with serious mental illnesses.

CHAPTER 3: Provides overall thesis objectives and individual project rational and aims.

CHAPTER 4: Describes the main methods used in the thesis and planned analyses.

CHAPTER 5: Describes the development, testing and implementation of a novel algorithm designed to detect long-term antipsychotic polypharmacy prescribing in secondary mental health care, through the use of electronic health records. The chapter is based on the following peer-reviewed paper "Kadra, G., Stewart, R., Shetty, H., Jackson, R. G., Greenwood, M. A., Roberts, A., Chang, C.-K., MacCabe, J. H., and Hayes, R. D. (2015). Extracting antipsychotic polypharmacy data from electronic health records: developing and evaluating a novel process. *BMC Psychiatry*, *15*(1), 166."

CHAPTER 6: Investigates socio-demographic, socioeconomic, clinical, and service-use predictors of long-term antipsychotic polypharmacy initiation in a population with serious mental illnesses. This chapter is based on the following peer-reviewed paper: “Kadra, G., Stewart, R., Shetty, H., Downs, J., MacCabe, J. H., Taylor, D., & Hayes, R. D. (2016). Predictors of long-term (≥ 6 months) antipsychotic polypharmacy prescribing in secondary mental healthcare. Schizophrenia Research, 174, 1-3.”

CHAPTER 7: Investigates whether receiving an antipsychotic polypharmacy prescription at the point of inpatient discharge is associated with future hospital readmissions into secondary mental health care.

CHAPTER 8: Investigates whether long-term prescribing of antipsychotic polypharmacy has an effect on the risk of death in patients with serious mental illness receiving treatment in South London and Maudsley mental health services. In addition, this chapter further investigates whether this risk varied depending on the cause of death and other factors such as antipsychotic dose.

CHAPTER 9: Considers all findings from the previous chapters in relation to existing research. I also discuss the strengths and limitations of the thesis and consider how my findings fit into the wider treatment context of patients with serious mental illnesses. I discuss further other possible implications and ideas for further research.

CHAPTER 1: BACKGROUND

1.1 Serious mental illnesses and detrimental health outcomes

The International Classification of Diseases, 10th edition (ICD-10) diagnoses of schizophrenia (F20.x), schizoaffective disorder (F25.x) and bipolar disorder (F31.x) are referred to as Serious Mental Illnesses (SMIs) due to their profound impact on individual's cognitive, affective, behavioural and physical state (Stahl 2013). In addition to having a significant effect on patients' day-to-day functioning, SMI diagnoses have also been associated with a number of detrimental health outcomes. For example, hospital readmission rates into mental health services are high amongst this population (Weiden & Olfson 1995; Schennach et al. 2012). Furthermore, individuals with SMI have an increased risk for physical health problems (Brown et al. 2000); for example, the prevalence of metabolic problems has been estimated to be approximately twice that of the general population (Reynolds & Kirk 2010). In addition, SMI diagnoses have been associated with an increased risk of dying prematurely from both natural (e.g. cardiovascular disease, respiratory disease) and unnatural (e.g. suicide, violence) causes, in comparison to the general population (Osby et al. 2000; Joukama et al. 2001; Joukama et al. 2006; Auquier et al. 2006; Chang et al. 2011). Natural causes of death are among the leading cause of mortality in SMI population, with a particularly increased risk for cardiovascular disease (Raedler 2010). Although factors such as suicide, accidents, violence and poor lifestyle choices (Brown et al. 2000; Auquier et al. 2006; Osborn et al. 2014) partially explain some of the above disparities, the underlying mechanisms remain unclear.

1.2 Antipsychotic medication

Antipsychotic medications have been the mainstay of treatment for SMI since the 1950s, for both acute episodes and maintenance management (Taylor et al. 2009). Although antipsychotics have complex psychopharmacological mechanisms and differ in their therapeutic actions (e.g. efficacy, tolerability) and side effects, they have been loosely categorized in two groups: first-generation (FGAs) (i.e. typical; older) and second-generation (SGAs)(i.e. atypical; newer) antipsychotics (British National Formulary 2015) based on broad psychopharmacological properties and their chronological origin.

Currently in the UK there are fourteen first-generation and eight second-generation antipsychotics available on prescription. The British National Formulary (BNF) (British National Formulary 2015) provides prescription guidance, including minimum and maximum recommended prescribing dose. Antipsychotic medications have been described as having 'the most complex pharmacological mechanisms of any drug class within the field of clinical psychopharmacology' (Stahl 2013, p.130). Although, the detailed psychopharmacological mechanisms of antipsychotic treatment are beyond the scope of this thesis, briefly first-generation antipsychotics are primarily dopamine D_2 receptor antagonists and target predominantly positive symptoms (Stahl 2013). FGAs have been associated with acute extrapyramidal side effects and hyperprolactinemia. SGAs refer to a group of antipsychotics that were introduced starting with clozapine (which was the first of the SGAs). They also target positive symptoms; however in contrast to FGAs, they have a serotonin-dopamine receptor antagonist action and have

been associated with lower levels of extrapyramidal side effects and hyperprolactinemia (Stahl 2013). However, SGAs have been associated with greater weight gain and metabolic problems, such as diabetes and dyslipidaemia (Stahl 2013; Daumit et al. 2008; Correll et al. 2009). Consequently patients with SMI frequently have physical health comorbidities (Auquier et al. 2006; Raedler 2010; Suzuki et al. 2014; Pramyothin & Khaodhiar 2010). In addition research has also indicated that SMI patients have an increased risk for comorbid diagnoses such as substance use, depression and personality disorder (Kreyenbuhl et al. 2007; Ganguly et al. 2004). As a result this population could experience psychotropic and/or physical health medication polypharmacy for comorbid physical and other (than SMI) mental health problems (Kreyenbuhl et al. 2007; Ganguly et al. 2004; Auquier et al. 2006; Raedler 2010; Suzuki et al. 2014; Pramyothin & Khaodhiar 2010). Studies on psychotropic and physical health medication polypharmacy are discussed in more detail in the Discussion section 9.7.

1.3 Antipsychotic medication and detrimental health outcomes

Antipsychotic medication prescribing has been one factor proposed to explain the health disparities observed between individuals diagnosed with a serious mental illness and the general population. In addition to the aforementioned side effects, some antipsychotics have been associated with increased mortality (Montout et al. 2002). For example, although research has been sparse, there is some evidence to suggest that FGAs are associated with a higher mortality rate from natural causes and suicide in comparison to patients who have not received antipsychotic medication (Kiviniemi et al.

2013; Joukama et al. 2006). Research examining SGAs has been more ambiguous. Olanzapine has been associated with an increased risk for natural causes of death such as cardiovascular disease (Raedler 2010) in comparison to other antipsychotics. However, clozapine has been associated with a decreased risk of premature death from both natural and unnatural causes in comparison to patients taking other antipsychotics (Hayes et al. 2014) and reduced risk of all-cause mortality compared to patients not taking antipsychotic medication (Kiviniemi et al. 2013). In addition, clozapine has been associated with reduced rehospitalisation (Valevski et al. 2012; Nielsen et al. 2012; Gee & Howes 2016). Further evidence has suggested that there is a variation in risk across different antipsychotic regimens. For example, patients prescribed two or more antipsychotics simultaneously (antipsychotic polypharmacy) have been found to have an increased risk for physical health problems (Ganguly et al. 2004; Brown et al. 2000; Kuo et al. 2011; Correll et al. 2007) and mortality (Waddington et al. 1998; Joukama et al. 2006) in comparison to patients prescribed monotherapy.

1.4 Treatment guidelines

Existing prescribing guidelines (NICE & NCCMH 2013; APA 2010) have been a pivotal reference point in clinical decision-making, by advocating evidence-based approaches to medication prescription for SMIs. These guidelines are mostly derived from randomised controlled trials of antipsychotic medication, which are recognized as the ‘gold standard’ for establishing antipsychotic efficacy, although these may have limited statistical power to investigate rare

outcomes, relatively short duration of follow-up and limited generalizability for assessing risk.

Current guidelines (NICE & NCCMH 2013) for the management of SMIs recommend that a patient is trialled on a single antipsychotic after a careful consideration of antipsychotic side effects, medical history and baseline physical examination, such as weight, waist circumference, pulse and blood pressure, blood glucose, blood lipid profile, prolactin levels and assessment of lifestyle factors (e.g. diet and physical activity). A patient whose illness has not responded to "the sequential use of adequate doses of at least two different antipsychotic drugs (at least one of the drugs should be a non-clozapine second-generation antipsychotic)" (NICE 2006, section 1.5.7.2) should be offered clozapine. If a non-response to an optimized clozapine treatment is further noted, NICE (NICE & NCCMH 2013) recommends that a clozapine augmentation should be initiated with another antipsychotic (i.e. clozapine polypharmacy). An adequate trial of an antipsychotic is defined as lasting for a minimum of 8 to10 weeks (Morrissette & Stahl 2014; Taylor et al. 2011; Correll et al. 2009; Paton et al. 2008). According to these guidelines, it is only as a last resort that two non-clozapine antipsychotics should be prescribed concurrently, a situation also referred to as antipsychotic polypharmacy. However, observational studies (Suokas et al. 2012; Sim et al. 2004) investigating medication prescribing in clinical settings have highlighted that randomised controlled trials poorly reflect 'real-life' clinical practice and decision-making, as they operate in an idealized environment and investigate medication administration in restricted populations and over limited time

spans. Furthermore, contrary to existing guidelines that recommend antipsychotic polypharmacy as the last alternative in treatment for schizophrenia (NICE & NCCMH 2013), polypharmacy is often introduced prior to the recommended trialling of two separate antipsychotics and clozapine (Lochmann van Bennekom et al. 2013).

1.5 Antipsychotic polypharmacy prevalence

Aside from clozapine polypharmacy, which has modest evidence of effectiveness, albeit mostly derived from open-label trials (Freudenreich & Goff 2002; Taylor et al. 2011), there is currently no evidence to indicate that antipsychotic polypharmacy is more effective as treatment than a single antipsychotic (i.e. monotherapy). However, contrary to existing guidelines and recommendations, observational studies have estimated that in real-life clinical practice, polypharmacy prevalence varies between 10-30% (Gallego et al. 2012; Freudenreich & Goff 2002) with a global median estimated at 19.6% (Gallego et al. 2012). Antipsychotic polypharmacy prevalence significantly differs across countries, with US, Europe and Oceania having a higher prevalence in comparison to Asia (Gallego et al. 2012). In the UK, amongst the SMI population, polypharmacy prevalence has been estimated at 38% in inpatient populations and 16% in individuals living in the community (Mace & Taylor 2015; Patel et al. 2014).

1.6 Clinical rationale for antipsychotic polypharmacy prescribing

The disparity between clinical recommendations and practice has brought considerable attention to antipsychotic polypharmacy. Research examining

the clinical rationale behind its prescribing has indicated that polypharmacy is frequently prescribed for the following reasons:

i) to manage clinical symptoms after the failure of previous monotherapy including clozapine (Lochmann van Bennekom et al. 2013; Barnes & Paton 2011b);

ii) when switching from one drug to another (Barnes & Paton 2011b);

iii) to deal with side effects of monotherapy such as extrapyramidal side effects (Barnes & Paton 2011b; Grech & Taylor 2012; Miller & Craig 2002);

iv) to target particular symptoms such as aggression and negative symptoms, or to target residual clinical symptoms (Grech & Taylor 2012);

v) to achieve more rapid response (Miller & Craig 2002; Barnes & Paton 2011a);

vi) to avoid high dosing with one antipsychotic (Barnes & Paton 2011b; Langan 2010);

vii) when a combination that has been planned for the short term is continued as the patient has become ‘stuck in switching’ (this term has been used to indicate that polypharmacy is a consequence of a planned cross-titration, where following mental health deterioration due to medication switching, the patient has remained on two or more antipsychotics) (Barnes & Paton 2011b).

viii) as a result of a patient declining clozapine

1.7 Measuring antipsychotic polypharmacy

To date, there have been substantial differences in measuring antipsychotic polypharmacy, ranging from studies that have specified no temporal parameters for concurrent antipsychotic use (Misawa et al. 2011; Sim, Su, Chan, et al. 2004; Janssen et al. 2005), to studies that have specified concomitant prescribing for at least 28 days (Jaffe & Levine 2003), 6 weeks (Taylor et al. 2002; Broekema et al. 2007), 60 days (Suokas et al. 2012; Ganguly et al. 2004), and 90 or more days (Barbui et al. 2006; Kreyenbuhl et al. 2007). Consequently, comparing findings between studies has been very difficult. Furthermore, although existing guidelines [e.g. Maudsley Prescribing Guidelines (Taylor et al. 2009)] recommend a trial with a minimum duration of 8-10 weeks in order to establish antipsychotic efficacy and observe treatment effect (Morrissette & Stahl 2014; Taylor et al. 2011; Correll et al. 2009; Paton et al. 2008), there has been a considerable paucity of research examining antipsychotic polypharmacy of longer duration and where a polypharmacy regimen is prescribed as a regular treatment.

One of the most significant limitations to measuring polypharmacy of shorter duration has been the difficulty in distinguishing between polypharmacy that is intended as a regular treatment regimen and medication that is administered as required, otherwise known as *pro re nata* (PRN). Evidence from a UK audit (Paton et al. 2008) indicated that approximately 75.8% of antipsychotic polypharmacy prescriptions include PRN medication. Furthermore PRN medication has been cited as the prime cause for the high prevalence of polypharmacy and high-dose prescribing (Paton et al. 2008; Milton et al.

1998; Mace & Taylor 2015). An additional problem encountered by studies examining polypharmacy over short periods of time is the likely detection of antipsychotic cross-titration; otherwise known as 'switching'. Switching between one antipsychotic to another involves short-periods of concomitant antipsychotic use, which is usually resolved within 10 weeks (Lochmann van Bennekom et al. 2013; Correll et al. 2009). Thus, including cross-titration as part of polypharmacy would yield an inflated prevalence and would not reflect regimens that are intended as regular long-term treatments. Lastly, antipsychotic polypharmacy has been largely examined amongst inpatient populations, where it is very prevalent, partly due to PRN medication and medication cross-titration (Jaffe & Levine 2003; Centorrino et al. 2004; Gallego et al. 2012; Broekema et al. 2007). Therefore, it is imperative to examine antipsychotic prescribing beyond an inpatient population.

1.8 Conclusions

Antipsychotic medication prescribing has been proposed as one of the contributing factors to the health disparities observed between patients with SMI and the general population (Montout et al. 2002; Kiviniemi et al. 2013; Raedler 2010). However, research has also suggested that there are significant variations across antipsychotic treatment regimens and negative outcomes (Galling et al. 2017). These findings are even more disconcerting in view of evidence that this regimen remains common in clinical practice across services, countries and time (Gallego et al. 2012; Paton et al. 2008) and despite a lack of empirical support and explicit recommendations against its use by existing guidelines (APA 2010; NICE & NCCMH 2013). Existing

research that has tried to examine antipsychotic polypharmacy prescribing in real-life clinical settings has been plagued by inconsistencies with defining and measuring this regimen, thus making it almost impossible to draw any definitive conclusions regarding the predictors and long-term consequence of this regimen (Boaz et al. 2013; Katona et al. 2014; Tiihonen et al. 2012; Waddington et al. 1998). In chapter 2, I review existing literature in detail examining long-term antipsychotic polypharmacy.

CHAPTER 2: LITERATURE REVIEW

2.1 Aim

The aim of this review was to examine all observational studies that have investigated predictors and outcomes of long-term antipsychotic polypharmacy; and to draw conclusions taking into account methodological limitations.

2.2 Background

There are four previous papers that have reviewed literature on antipsychotic polypharmacy (Langan & Shajahan 2010; Lochmann van Bennekom et al. 2013; Correll & Gallego 2012; Weinmann et al. 2009), including one very recent systematic review and meta-analysis that focused specifically on antipsychotic augmentation and its efficacy (Galling et al. 2017). However, to date there has been no review examining literature on predictors and consequences of long-term antipsychotic polypharmacy. Examining long-term concomitant antipsychotic prescribing is important for several reasons. Kreyenbul and colleagues (Kreyenbuhl et al. 2006) reported that cross-sectional definitions of antipsychotic polypharmacy do not accurately reflect or identify patients receiving regular long-term polypharmacy and omit between 32 and 89 percent of this population. This is mainly due to cross-sectional methods identifying a high proportion of false positive cases (i.e. PRN medication and medications cross-titration) that are primarily consisting of short-term polypharmacy and a population with entirely different characteristics. Furthermore, studies looking for co-prescription of antipsychotic medications over short-periods (e.g. one day census) also risk omitting cases of polypharmacy where concomitant medications are

mentioned separately (e.g. in separate documents few days apart), although the prescriptions overlap in time (Harrington 2002). As a result, we currently have a poor understanding of whether certain groups are more likely to receive antipsychotic polypharmacy.

Furthermore, we have been unable to estimate accurately the potential consequences of this medication regimen. This is especially important when we take into consideration existing literature indicating that patients with SMI diagnoses who use antipsychotic medications have a high risk for mental health hospital readmissions (Weiden & Olfson 1995; Schennach et al. 2012), physical health problems and death (Reininghaus et al. 2015; Joukama et al. 2001; Saha et al. 2007), more specifically natural causes of death such as sudden cardiac death (Ray et al. 2009; Koponen et al. 2008; Osby et al. 2000). Antipsychotic polypharmacy has been found to increase particularly the risk of sudden cardiac death (Joukama et al. 2006; Waddington et al. 1998; Procyshyn et al. 2001; Centorrino et al. 2004) as compared to monotherapy. However, existing literature reviews have all included the examinations of studies of unspecified or short duration polypharmacy (typically an antipsychotic polypharmacy duration of 10 weeks or more is required, in order to be able to exclude cross-titration) (Langan & Shajahan 2010; Lochmann van Bennekom et al. 2013; Correll & Gallego 2012; Weinmann et al. 2009). Consequently, research has potentially been subject to misclassification. In addition, confounding by indication is also an important issue to consider if we are to provide evidence to conclude that the observed associations can be attributed to polypharmacy prescribing alone.

Confounding by indication here refers to a type of confounding where patients prescribed antipsychotic polypharmacy are inherently different from those who are prescribed only one antipsychotic.

In this literature review, I aimed to examine observational studies, as opposed to randomised control trials. Randomised controlled trials focus on establishing drug efficacy i.e. the performance of a medication under ideal circumstances. Observational studies however, have the potential to investigate effectiveness, which is the performance of a medication under real-world circumstances (Singal et al. 2014). Furthermore, antipsychotic polypharmacy randomised controlled trials are generally sparse due to difficulty in prescribing the same combination and dose of antipsychotics to a larger number of patients. Antipsychotic co-prescription is often done after careful consideration of a number of different factors such as patient's age, health and lifestyle (NICE & NCCMH 2013). Furthermore, at present little is known about the exact mechanisms and interactions between different antipsychotics, therefore there is potentially increased risk for side effects (Auquier et al. 2006; Raedler 2010; Suzuki et al. 2014; Pramyothin & Khaodhiar 2010). As a result, clinical trials are often difficult to plan and implement. Although there have been some clinical trials investigating polypharmacy, they have predominantly considered clozapine augmentation (Freudenreich & Goff 2002; Lochmann van Bennekom et al. 2013). Furthermore, due to limited time of follow-up, such studies are not able to investigate rarer outcomes such as death. In addition, randomised controlled trial population samples are often carefully selected and matched on a

number of factors, thus making it impossible to establish predictors of this regimen in real-life clinical settings. Lastly, observation studies provide a unique opportunity to obtain a true representation of real-world clinical practice, patterns and outcomes, in contrast to randomised clinical trials.

2.3 Methods

2.3.1 Search strategy

Relevant publications were ascertained by entering the following search terms into PubMed and Ovid (Embase; PsycINFO; Ovid Medliner; International Pharmaceutical Abstracts) engines: 'serious mental illness' OR 'schizophrenia' OR 'schizoaffective' OR 'bipolar' AND 'antipsychotic' AND 'polypharmacy' OR 'combination' OR 'polytherapy' OR 'concomitant' OR 'addition' OR cotreatment' OR 'adjunctive' OR 'concurrent' OR 'simultaneous'.

2.3.2 Inclusion criteria

I considered all cross-sectional and longitudinal observational studies of antipsychotic polypharmacy that were published in English, irrespective of their publication date, country of origin, and that operationalized the definition of 'long-term polypharmacy' by restricting the review to studies that explicitly ascertained and considered polypharmacy duration of at least 60 days. Most of the existing research in this field has rarely examined a minimum duration of polypharmacy of more than 60 days, therefore choosing studies with an antipsychotic duration over 60 days would have significantly limited the

number of studies I can review. Furthermore, polypharmacy of 60 days should be able to exclude most cases of cross-titration (see above and Chapter 1 section 1.7). Therefore, it was considered an adequate definition of long-term polypharmacy for the purpose of this review. Studies that did not specify the duration of polypharmacy, but which investigated patients discharged from hospital on two or more antipsychotics, were included. The main rationale for this is that this group was unlikely to be undergoing cross-titration, as this is normally completed prior to discharge. Furthermore, the concomitant prescribing was very likely to have commenced some time before discharge and therefore, polypharmacy would reflect an intended regular treatment. Studies that did not include information on the length of concomitant prescribing were not considered, as they were most likely to include shorter forms of polypharmacy (e.g. PRN medication; cross-titration), based on examining existing literature in this field. The only exception to this rule was one meta-analysis (Gallego et al. 2012); although this did not only focus on antipsychotic polypharmacy duration of 60 or more days, it did exclude studies that did not provide specific information on the definition of polypharmacy. This meta-analysis included seven of the studies referenced in Table 2.1. (Barbui et al. 2006; Biancosino et al. 2005; Clark et al. 2002; Faries et al. 2005; Ganguly et al. 2004; Morrato et al. 2007; Kreyenbuhl et al. 2007). Systematic literature reviews that had not conducted a meta-analysis, and randomized controlled trials, were not included in this review.

2.4 Results

2.4.1 Overview

The search terms described above detected 883 papers. Out of those 739 were excluded based on their title and abstract (this was mainly due to not investigating long-term antipsychotic polypharmacy) or because they were a duplicate. I excluded a further 126 as they did not satisfy the inclusion criteria, leaving a total of 18 research papers.

Overall, six studies were based on data derived from insurance medical databases, four had derived data from national registers, seven had used data derived from clinical records, and one was a meta-analysis.

The results section of this chapter catalogues these studies; whereas their interpretation, strengths and limitations will be discussed in the discussion section of this chapter (see page 66).

Table 2.1 summarises published research that has investigated prevalence, predictors or consequences of concomitant antipsychotic prescribing for 60 or more days, in patients with SMI. The table includes information about the primary author, year and country the study was carried out in. In addition, the sample size, data source (e.g. medication prescription database, clinical records), study design, inclusion criteria and definition of antipsychotic polypharmacy are included.

Table 2.1 Summary of literature examining long-term antipsychotic polypharmacy prescribing.

Study	Country	Sample size	Data source	Study design and inclusion criteria	Antipsychotic polypharmacy definition
Baandurp et al., 2010	**Denmark**	2,130	Danish Central Register	Population nested case-control study, including adults with schizophrenia or non-affective psychotic disorder, who had at least one antipsychotic prescription and had been hospitalised for less than 240 days in the year prior to death. All cases and control were gender and age matched, and had to have had their first entry on the register at least 365 days prior to the date of death. Patients with bipolar disorder were excluded.	≥2 antipsychotics in the 90 days prior to death
Barbui et al., 2006	**Four European Countries (UK, Italy, Netherlands, Germany)**	375	QUATRO study (Quality of Life following Adherence Therapy for People Disabled by Schizophrenia and their Carers)	Prospective cohort study, including patients diagnosed with schizophrenia; clinical instability in the year before assessment; need for antipsychotic in the year after the assessment. Patients with learning disability, organic brain disorder; forensic psychiatric service; alcohol or drug	≥2 antipsychotics at baseline and at follow-up (12 months later)

Study	Country	Sample size	Data source	Study design and inclusion criteria	Antipsychotic polypharmacy definition
				dependence; inability to speak local language; and lack of capacity to consent, were excluded.	
Biancosino et al., 2005	**Italy**	354	Clinical records	Prospective cohort study including adult patients with any mental health diagnosis (excluding mental retardation) who were receiving antipsychotic treatment at discharge.	≥2 antipsychotics at inpatient discharge
Boaz et al., 2013	**US**	3,563	Medicaid - medical claims database	Longitudinal cohort study, including Medicaid enrolees from Florida between 2004-2008 satisfying the antipsychotic polypharmacy criteria.	≥2 antipsychotics for ≥60 days
Clark et al., 2002	**US**	836	Medicaid - medical claims database	Cohort study between 1995 and 1999, of patients with schizophrenia and schizoaffective disorder. Patients with diagnoses of Alzheimer's disease and mental	≥2 antipsychotics for 9 or more months

Study	Country	Sample size	Data source	Study design and inclusion criteria	Antipsychotic polypharmacy definition
				retardation were excluded.	
Faries et al., 2005	**US**	796	Schizophrenia Care and Assessment Programme	Non-randomised naturalistic prospective study between 1997 and 2003, of adult patients with SMI. Patients who were unable to consent to participate or that had participated in a clinical drug trial within 30 days prior to enrolment were excluded.	≥2 antipsychotics for more than 60 days
Gallego et al., 2012	**US**	1,418,163	Meta-analysis	Meta-analysis including studies that reported frequency of concomitant use of two or more antipsychotics, in adult patients. Exclusion: interventions studies aimed at decreasing polypharmacy; studies without specific information on polypharmacy.	≥2 antipsychotics
Ganguly et al., 2004	**US**	31,435	Medicaid - medical claims database	Longitudinal cohort study, including adult patients with schizophrenia with at least one claim under Medicaid between	≥2 antipsychotics for ≥61 days

Study	Country	Sample size	Data source	Study design and inclusion criteria	Antipsychotic polypharmacy definition
				January 1998 and December 2000 in Georgia and California.	
Grech and Taylor 2012	**UK**	38	South London and Maudsley (SLAM) prescription charts	Cohort study including inpatients and outpatients who had their medication supplied by SLAM. Patients prescribed clozapine polypharmacy were excluded.	≥2 antipsychotics for 6 or more months
Katona et al., 2014	**Hungary**	5,480	Insurance records	Longitudinal cohort study including adults with schizophrenia or schizoaffective disorder diagnosis and at least one antipsychotic medication record between 2007 and 2009.	2 antipsychotics for ≥60 days
Kreyenbuhl et al., 2007	**US**	61,257	The Veterans Health Administration (VHA) electronic health records	A longitudinal cohort study of patients with schizophrenia or schizoaffective disorder who fulfilled the antipsychotic polypharmacy criteria	≥2 antipsychotics for ≥90 days
Langle et al., 2012	**Germany**	374	ELAN study - health records	Prospective cohort study, including adult patients with schizophrenia or schizoaffective	≥2 antipsychotics before discharge and at four and six

Study	Country	Sample size	Data source	Study design and inclusion criteria	Antipsychotic polypharmacy definition
				disorder, using quetiapine, olanzapine, or risperidone for a minimum of 12 months. Exclusion: substance use diagnosis, organic psychiatric disorder, learning disability.	months later
Moilanen et al., 2016	**Finland**	53	Northern Finland Birth Cohort - clinical records	Longitudinal cohort study, investigating all adults with schizophrenia spectrum disorder.	≥2 antipsychotics, length of prescribing classified as a proportion of the follow-up time (three categories)
Morrato et al., 2007	**US**	55,481	Medicaid - medical claims database	Longitudinal cohort study including Medicaid enrolees in 5 states (California, Nebraska, Oregon, Utah, Wyoming), with at least one antipsychotic and a mental health diagnosis between 1998 and 2003.	≥2 antipsychotics for ≥60 days
Nielsen et al., 2010	**Denmark**	13,600	Danish Central Psychiatric Research Registry	Cohort study including patients diagnosed with schizophrenia for the first time between 1996	≥2 antipsychotic prescriptions renewed within a 4

Study	Country	Sample size	Data source	Study design and inclusion criteria	Antipsychotic polypharmacy definition
				and 2005.	month period
Ortiz et al., 2016	**US**	86,034	Medicaid - medical claims database	Cross-sectional study, all adult patients discharged from inpatient hospital between 1 January-31st December 2011.	≥2 antipsychotics at inpatient discharge
Santone et al., 2011	**Italy**	1,022	Hospital records (PROGRES-Acute project)	Cross-sectional study investigating all patients scheduled to be discharged from in-patient facilities.	≥2 antipsychotics at inpatient discharge
Suokas et al., 2012	**Finland**	16,083	Finnish National Hospital Discharge Register	Cross-sectional study including all adults in Finland with at least one hospitalisation (2000 - 2007) due to schizophrenia and who were alive on 1 March 2007.	≥2 antipsychotics for ≥60 or more days

2.4.2 Predictors of antipsychotic polypharmacy

Table 2.2 summarises research selected from Table 2.1. that has investigated predictors of antipsychotic polypharmacy, in patients with SMI. The table includes information about the primary author and year, main predictors the study investigated, the results and confounders that were adjusted for in the analysis.

Table 2.2 Summary of literature examining predictors of long-term antipsychotic polypharmacy prescribing.

Factors	Author and main results
Age	**Gallego et al., 2012** found no association between antipsychotic polypharmacy and age (Spearman's rho r=-0.09; p=0.31). **Kreyenbuhl et al., 2007** found younger patients were more likely to receive polypharmacy (OR= 0.99; 95% CI: 0.98-0.99) than monotherapy. *Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index.* **Morrato et al., 2007** found that patients younger than 17 and older than 35 were less likely to receive polypharmacy in comparison to patients aged between 18 and 24. *Adjusted for: age, sex, ethnicity, mental health diagnosis, current substance use, mental health-related hospitalisation, state program, year of index prescription, index antipsychotic drug.* <17 (OR=0.60; 95%CI: 0.49- 0.74) 18-24 (1.0) 25-34 (OR=0.92; 95%CI: 0.76-1.10) 35-44 (OR=0.79; 95%CI: 0.66-0.95) 45-54 (OR=0.76; 95%CI: 0.64- 0.92) 55-64 (OR=0.65; 95%CI: 0.51- 0.82) >65 (OR=0.38; 95%CI: 0.22- 0.66) **Ortiz et al., 2016** found that patients aged between 35 to 44 had an increased risk for polypharmacy as compared to patients aged 18-24 (OR=1.09, 95% CI: 1.01- 1.19). *Adjusted for: gender, age, length of stay and mental health diagnosis*

	Santone et al., 2011 reported no difference in age between patients prescribed polypharmacy and monotherapy (t=-0.929; p>0.05). **Suokas et al., 2012** Age in chronic schizophrenia patients was not associated with antipsychotic polypharmacy (reporting Crude Odds Ratios). <25 (1.0) 26-35 (OR=0.76; 95% CI: 0.39- 1.47) 36-45 (OR=0.77; 95% CI: 0.40- 1.48) 46-55 (OR=0.81; 95% CI: 0.42- 1.55) 56+ (OR=0.56; 95% CI: 0.29- 1.07) Patients aged 46 and over and who had a recent onset schizophrenia, had a lower risk for polypharmacy prescribing. <25 (1) 26-35 (OR=1.03; 95% CI: 0.85- 1.25) 36-45 (OR=0.88; 95% CI: 0.72- 1.07) 46-55 (OR=0.81; 95% CI: 0.67- 0.99) 56+ (OR=0.62; 95% CI: 0.50- 0.75)
Gender	**Gallego et al., 2012** found no association between being male and the likelihood of receiving polypharmacy (Spearman's rho r=0.16; p=0.05). **Ganguly et al., 2004** found that being male was associated with increased risk for antipsychotic polypharmacy **(**OR=1.15; 95% CI: 1.02- 1.29; p=0.0197). *Adjusted for: 40 variables of the following categories: age, gender, disability, comorbid diagnosis, dug class, antipsychotic medication, health care utilisation.*

	Kreyenbuhl et al., 2007 reported no difference in risk for polypharmacy and monotherapy between genders **(**OR=1.1; 95%CI: 0.92-1.19). *Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index.* **Morrato et al., 2007** found that men were more likely to receive polypharmacy than women (OR=1.26; 95% CI: 1.14-1.39). *Adjusted for: age, sex, ethnicity, mental health diagnosis, current substance use, mental health-related hospitalisation, state program, year of index prescription, index antipsychotic drug.* **Ortiz et al., 2016** found that male patients did not have an increased risk for polypharmacy (OR=1.00, 95% CI: 0.95- 1.05). *Adjusted for: gender, age, length of stay and mental health diagnosis* **Santone et al., 2011** reported males were more likely to be prescribed polypharmacy than monotherapy (x^2= 4.99; p =0.026). **Suokas et al., 2012** for chronic schizophrenia patients being male was associated with increased risk for polypharmacy (OR=1.25; 95% CI: 1.13-1.4). For patients with recent onset schizophrenia, being male was also associated with increased risk for polypharmacy (OR=1.33; 95% CI: 1.2-1.47)(reporting Crude Odds Ratios).
Ethnicity	**Gallego et al., 2012** found no association between being white and antipsychotic polypharmacy prescribing (Spearman's rho r=-0.23; p=0.20). **Kreyenbuhl et al., 2007** found that African Americans were less likely to receive polypharmacy as compared to Whites (OR=0.81; 95%CI: 0.75-0.87).

	Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index. **Morrato et al., 2007** found that Asian patients (OR=1.55; 95% CI: 1.17- 2.04) were at increased risk for polypharmacy in comparison to white patients. *Adjusted for: age, sex, ethnicity, mental health diagnosis, current substance use, mental health-related hospitalisation, state program, year of index prescription, index antipsychotic drug.*
Marital status	**Kreyenbuhl et al., 2007** found that married patients were less likely to receive polypharmacy than monotherapy (OR=0.84; 95%CI: 0.78- 0.90). *Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index.* **Santone et al., 2011** single patients were more likely to be prescribed polypharmacy than monotherapy (x^2= 11.18; p=0.048). **Biancosino et al., 2005** marital status did not predict antipsychotic polypharmacy prescribing (p=0.44). *Adjusted for: antipsychotic polypharmacy on admission, positive symptoms on admission, manic/hostility symptoms, education.*
Employment	**Barbui et al., 2006** found no association between employment status and polypharmacy (OR=2.46; 95% CI: 0.67- 9.04). *Adjusted for: living status, accommodation, length of antipsychotic therapy, number of antipsychotic drugs in past 12 months, BPRS disorganisation, BPRS depression, BPRS negative symptoms, study site, number of antipsychotic drugs.*

	Biancosino et al., 2005 found that not being employed was associated with increased risk for polypharmacy (OR=3.10; 95% CI: 1.06- 9.09). *Adjusted for: antipsychotic polypharmacy on admission, positive symptoms on admission, manic/hostility symptoms, education.* **Santone et al., 2011** reported no difference in occupational status between patients prescribed polypharmacy and monotherapy (x^2= 9.52; p>0.05).
Clinical symptoms	**Barbui et al., 2006** found no association between BPRS negative symptoms and polypharmacy (OR=0.86; 95% CI: 0.72- 1.02). *Adjusted for: employment, living status, accommodation, length of antipsychotic therapy, number of antipsychotic drugs in past 12 months, BPRS disorganisation, BPRS depression, study site, number of antipsychotic drugs.* **Biancosino et al., 2005** found that BPRS positive symptoms of admission were associated with increased risk for polypharmacy (OR=1.06; 95% CI: 1.01- 1.12). *Adjusted for: antipsychotic polypharmacy on admission, employment, education.* **Gallego et al., 2012** found no association between clinical symptoms and receiving polypharmacy prescription (Spearman rho). Baseline Clinical Global Impression score (r=0.54; p=0.27) Total PANSS score (r=0.10; p=0.87) Positive PANSS score (r=-0.60; p=0.40) Negative PANSS score (r=-0.80; p=0.20) Total BPRS score (r=0.03; p=0.96) GAF score (r=0.74; p=0.26)

	Moilanen et al., 2016 indicated that polypharmacy was associated with poorer functioning (SOFAS) (p= 0.002); poor remission (PANNS) (p=0.003); and poor clinical outcome (CGI) (p=0.002) (Chi^2 test values have not been reported by the study). *Adjusted for: psychiatric hospital days, length of follow-up, long-term dose-years.*
Comorbid diagnosis	**Ganguly et al., 2004** reported that comorbid alcohol (OR=0.58; 95%CI: 0.36- 0.93; P=0.0237) and comorbid personality disorder (OR=0.71; 95%CI: 0.55- 0.92; P=0.0082) were associated with lower risk for polypharmacy. *Adjusted for: 40 variables of the following categories: age, gender, disability, comorbid diagnosis, dug class, antipsychotic medication, health care utilisation.* **Kreyenbuhl et al., 2007** found that patients with comorbid depression (OR=0.83; 95%CI: 0.78-0.90); and comorbid substance use (OR=0.90; 95% CI: 0.83- 0.97) were less likely to receive polypharmacy. *Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index.* **Morrato et al., 2007** found that substance abuse was not associated with increased likelihood for polypharmacy prescription (OR=0.91; 95% CI: 0.82- 1.02). *Adjusted for: age, sex, ethnicity, mental health diagnosis, current substance use, mental health-related hospitalisation, state program, year of index prescription, index antipsychotic drug.*
Inpatient admission	**Gallego et al., 2012** found that patients who have had a previous inpatient stay were more likely to receive polypharmacy than other patients (Mann-Whitney test p<0.001). **Ganguly et al., 2004** reported that psychiatric inpatient episodes in the previous six months were associated with increased risk for polypharmacy (OR=1.42; 95%CI: 1.17-1.73; P=0.0004).

	Adjusted for: 40 variables of the following categories: age, gender, disability, comorbid diagnosis, dug class, antipsychotic medication, health care utilisation. **Kreyenbuhl et al., 2007** found patients with more previous psychiatric admissions were more likely to receive polypharmacy than monotherapy (OR=1.63; 95%CI: 1.52- 1.74). *Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index.* **Ortiz et al., 2016** length of inpatient stay of <90 days as compared to < 7days was associated with an increased risk for polypharmacy (OR=5.53, 95% CI: 5.01- 6.11). *Adjusted for: gender, age, length of stay and mental health diagnosis*
Outpatient contact	**Ganguly et al., 2004** reported that the number of psychiatric outpatient visits in the previous 6 months were associated with increased risk for polypharmacy (OR=1.03; 95%CI: 1.01- 1.05; P=0.0061). *Adjusted for: 40 variables of the following categories: age, gender, disability, comorbid diagnosis, dug class, antipsychotic medication, health care utilisation.* **Kreyenbuhl et al., 2007** found that patients with more outpatient mental health visits were more likely to receive polypharmacy than monotherapy (OR=1.003; 95% CI: 1.002-1.003). *Adjusted for: age, gender, race, marital status, disability status, diagnosis, depression, substance use, PTSD, psychiatric hospitalisation in the past year, total outpatient mental health visits, score on Charlson Index.*
Previous medication use	**Barbui et al., 2006** found that the number of antipsychotic drugs previously used was associated with increased risk for polypharmacy (OR=144.4; 95% CI: 31.9- 654.4). *Adjusted for: employment, living status, accommodation, length of antipsychotic therapy, BPRS disorganisation, BPRS depression, BPRS negative symptoms, study site, number of antipsychotic*

drugs.

Gallego et al., 2012 found that patients who have received long-acting injectable antipsychotic (LAI) were more likely to receive polypharmacy (Spearman's rho r=0.26; p=0.04).
Clozapine treatment had no association with polypharmacy (Mann-Whitney test p=0.24).

Ganguly et al., 2004 reported that clozapine use (OR=11.77; 95%CI: 9.23- 15.01; P<0.0001) and regular antipsychotic use (OR= 4.84; 95%CI: 4.21- 5.57; P<0.0001) were associated with increased risk for polypharmacy.
Adjusted for: 40 variables of the following categories: age, gender, disability, comorbid diagnosis, dug class, antipsychotic medication, health care utilisation.

Morrato et al., 2007 found that clozapine was not associated with increased risk for polypharmacy (OR=1.59; 95% CI: 0.96- 2.64).
Adjusted for: age, sex, ethnicity, mental health diagnosis, current substance use, mental health-related hospitalisation, state program, year of index prescription, index antipsychotic drug.

Suokas et al., 2012
For patients with chronic schizophrenia, previous use of antipsychotics was associated with increased risk for polypharmacy (percentage indicates quartiles by the number of purchased prescriptions)(reporting Crude Odds Ratios).

0-25% (1.0)
25-50% (OR=3.35; 95% CI: 2.79-4.03)
50-75% (OR=6.86; 95% CI: 5.72- 8.23)
75-100% (OR=15.04; 95% CI: 12.46- 18.16)

For recent onset schizophrenia, previous use of antipsychotics was associated with increased risk for polypharmacy ('percentage indicates quartiles by the number of purchased prescriptions).

	0-25% (1.0) 25-50% (OR=2.72; 95% CI: 2.38- 3.11) 50-75% (OR=5.73; 95% CI: 4.95- 6.62) 75-100% (OR=11.11; 95% CI: 9.38- 13.16)

Age

Age has been extensively investigated by previous studies; however evidence appears mixed. One large US cohort study (Ortiz et al. 2016)(N=86,034) reported that patients aged between 35 and 44 years are more likely to be prescribed antipsychotic polypharmacy, as compared to patients aged 18-24 years (OR=1.09, 95% CI: 1.01- 1.19). However, evidence from a meta-regression including 147 studies and 1,418,163 patients indicated that age did not seem to be associated with antipsychotic polypharmacy prescribing (Spearman's rho r=-0.09; p=0.31) (Gallego et al. 2012). This finding was further supported by an Italian cohort study [(Santone et al. 2011); (t=-0.929; p>0.05)] examining mental health records of inpatients with SMI. A large Finnish register based study (Suokas et al. 2012) further drew a distinction between chronic and recent-onset schizophrenia outpatients and indicated that although age was not associated with antipsychotic polypharmacy in chronic schizophrenia, older age was associated with lower risk for polypharmacy in recent-onset schizophrenia outpatients (Suokas et al. 2012). A large US cohort study (Morrato et al. 2007) investigating patients eligible for mental health insurance (Medicaid) in five states, also reported that younger patients were at an increased risk for polypharmacy. Similarly, another large US study (n=45,571) investigating veterans clinical records, indicated that patients were more likely to receive polypharmacy as opposed to monotherapy if they were younger [(Kreyenbuhl et al. 2007); OR=0.99, 95% CI 0.98-0.99].

Gender

Evidence regarding the role of gender in predicting antipsychotic polypharmacy prescribing has also been mixed. Four large cohort studies reported that being male is associated with increased risk for antipsychotic polypharmacy prescribing (Santone et al. 2011; Morrato et al. 2007; Suokas et al. 2012; Ganguly et al. 2004). The first mentioned study above (Santone et al. 2011) examined a nationwide psychiatric inpatient sample in Italy (n=1,022) and found that males were more likely to receive antipsychotic polypharmacy (as opposed to antipsychotic monotherapy) than females (x^2= 4.99; p =0.026). The second study (Morrato et al. 2007) examined medical insurance records for 55,481 patients across five US states and found that men were more likely to receive a polypharmacy prescription (OR=1.26; 95% CI: 1.14-1.39). The third study similarly examined medical insurance records in two US states (Ganguly et al. 2004) and reported an association (OR=1.15; 95% CI: 1.02- 1.29; p=0.0197) between male gender and polypharmacy. A fourth study (Suokas et al. 2012) examined 16,083 schizophrenia outpatients in Finland using a national health register and similarly found that males were more like to be prescribed antipsychotic polypharmacy (OR=1.25; 95% CI: 1.13-1.4). However, three studies also found no evidence to indicate that gender had an effect on the likelihood to receive polypharmacy prescription. Ortiz et al. (Ortiz et al. 2016) examined 86,034 inpatients at discharge, nationally across the US and found that males were no more likely to receive polypharmacy than female patients (OR=1.00, 95% CI: 0.95- 1.05). Similarly, a large Veterans Affairs US study also reported no difference in risk between being prescribed antipsychotic polypharmacy or monotherapy across the

genders (OR=1.1, 95% CI: 0.92-1.19)(Kreyenbuhl et al. 2007). Evidence from a large meta-analysis (Gallego et al. 2012) investigating 1,418,163 patients across 147 studies also found no association (Spearman's rho r=0.16; p=0.05).

Ethnicity

Three large studies (Morrato et al. 2007; Gallego et al. 2012; Kreyenbuhl et al. 2007) investigated the association between ethnicity and antipsychotic polypharmacy prescribing. Morratto and colleagues (Morrato et al. 2007) investigated 55,481 patients from the Medicaid insurance database in US and found that the risk for polypharmacy prescribing is higher in patients from Asian ethnic background as compared to patients from white ethnicities (OR=1.55; 95% CI: 1.17- 2.04). In contrast Kreynbhul (Kreyenbuhl et al. 2007) investigated 45,571 patients from the Veterans Health Administration records and detected a lower risk for patients from African American background, as compared to whites (OR=0.81; 95%CI: 0.75-0.87). In their meta-analysis, Gallego and colleagues (Gallego et al. 2012) included information from 147 studies across the continents, examining a total of 1,418,163 patients and found no evidence of an association between antipsychotic polypharmacy prescribing and white ethnicity.

Marital status

Three studies investigated antipsychotic polypharmacy prescribing and marital status (Santone et al. 2011; Kreyenbuhl et al. 2007; Biancosino et al. 2005). A small Italian study (Biancosino et al. 2005)(n=354) investigated the

clinical records of an inpatient sample, and found that marital status did not predict antipsychotic polypharmacy prescribing (p=0.44). A second Italian study (Santone et al. 2011) examining a larger sample (n=1,022) of inpatients in a different region, found that single patients were more likely to be prescribed antipsychotic polypharmacy than monotherapy (x^2= 11.18; p=0.048). Furthermore, findings from a large US study (Kreyenbuhl et al. 2007) examining veterans mental health clinical records, similarly indicated that married patients were less likely to receive polypharmacy than monotherapy (OR=0.84; 95%CI: 0.78- 0.90).

Employment/ social deprivation

Employment status has been the only socioeconomic factor that previous research has investigated. There were no studies that have investigated the association between social deprivation and antipsychotic polypharmacy. In total three studies investigated employment status and antipsychotic polypharmacy prescribing (Barbui et al. 2006; Biancosino et al. 2005; Santone et al. 2011). The first study (Santone et al. 2011) examined 1,022 inpatient in an Italian hospital and reported no difference in occupational status between patients prescribed polypharmacy and monotherapy (x^2= 9.52; p>0.05). Similarly, a study conducted across four European countries (UK, Italy, Netherland and Germany)(Barbui et al. 2006), including 375 individuals also reported no association between employment status and polypharmacy (OR=2.46; 95% CI: 0.67- 9.04). However, in their study, Biancosino and colleagues (Biancosino et al. 2005) investigated the clinical records of 354 inpatients and found evidence indicating that not being employed was

associated with increased risk for polypharmacy (OR=3.10; 95% CI: 1.06-9.09).

Comorbid diagnosis

Three large cohort studies examined comorbid diagnoses and their association with antipsychotic polypharmacy. The first study (Ganguly et al. 2004) examined the medical insurance records for 31,435 patients with schizophrenia and reported that comorbid alcohol (OR=0.58; 95%CI: 0.36-0.93; P=0.0237) and comorbid personality disorder (OR=0.71; 95%CI: 0.55-0.92; P=0.0082) were associated with lower risk for long-term antipsychotic polypharmacy. Another US study examining medical insurance across five US states (Morrato et al. 2007) for 55,481 patients found that substance abuse was not associated with increased likelihood for polypharmacy prescription (OR=0.91; 95% CI: 0.82- 1.02). A third large US study (Kreyenbuhl et al. 2007) examining the mental health records for 45,571 patients found that patients with comorbid depression (OR=0.83; 95%CI: 0.78-0.90); and comorbid substance use (OR=0.90; 95% CI: 0.83- 0.97) were less likely to receive polypharmacy.

Clinical symptoms

Overall, there was mixed evidence regarding the role of clinical symptoms in antipsychotic polypharmacy prescribing. In their meta-analysis encompassing 1,418,163 patients, Gallego and colleagues (Gallego et al. 2012) reported total psychopathology and positive and negative mental health symptoms [as measured by Positive and Negative Syndrome Scale (PANSS); Brief

Psychiatric Rating Scale (BPRS)] and functioning [as assessed by Global Assessment of Functioning (GAF) and Clinical Global Impression (CGI)] were not associated with antipsychotic polypharmacy (please refer to Table 2.2 for the individual results). A small study (Barbui et al. 2006) that investigated 375 patients over 4 countries also found no association between BPRS negative symptoms and polypharmacy (OR=0.86; 95% CI: 0.72- 1.02). On the other hand, one study (Moilanen et al. 2016) found that polypharmacy was associated with poorer remission of clinical symptoms (as measured by PANSS) (p=0.003), poor clinical outcomes (as measured by Clinical Global Impression) (p=0.002) and impaired functioning (as measured by The Social and occupational Functioning Assessment Scale) (p= 0.002). One further study also indicated that BPRS positive symptoms on admission predicted antipsychotic polypharmacy at discharge (Biancosino et al. 2005) (OR=1.06; 95% CI: 1.01- 1.12).

Previous inpatient stay

There were four studies that have investigated the association between inpatient admission and long-term antipsychotic polypharmacy prescribing (Gallego et al. 2012; Ganguly et al. 2004; Kreyenbuhl et al. 2007; Ortiz et al. 2016). Overall, existing studies consistently indicated that a pervious inpatient stay increases the risk for antipsychotic polypharmacy prescribing. Evidence from a large meta-analysis (Gallego et al. 2012) indicated that patients who have had previous inpatient stay are more likely to receive polypharmacy than other patients (p<0.001). This was further supported by a large US study investigating medical claims database for 31,435 patients (Ganguly et al.

2004), which reported that psychiatric inpatient episodes in the previous six months were associated with increased risk for polypharmacy (OR=1.42; 95%CI: 1.17-1.73; P=0.0004). Another, large US Medicaid study (Ortiz et al. 2016) also reported that this risk was particularly elevated for inpatient stay of 90 or more days (as compared to an inpatient stay of 7 or less days)(OR=5.53, 95% CI: 5.01- 6.11). The fourth study investigated US electronic health records from the Department of Veterans Affairs and found that patients with more previous psychiatric admissions were more likely to receive antipsychotic polypharmacy than monotherapy (OR=1.63; 95% CI: 1.52- 1.74)(Kreyenbuhl et al. 2007).

Previous outpatient visit

Two large US studies investigated the effect of outpatient contact on polypharmacy prescribing (Kreyenbuhl et al. 2007; Ganguly et al. 2004). Findings were consistent in reporting that as compared to monotherapy, patients were more likely to receive antipsychotic polypharmacy if they had more outpatient visits [(Ganguly et al. 2004)(OR=1.03; 95% CI: 1.01- 1.05; P=0.0061); (Kreyenbuhl et al. 2007)(OR=1.00; 95% CI: 1.002-1.003)].

Previous community treatment orders (CTOs)

CTOs are part of the UK Mental Health Act. They are indicators of treatment non-adherence, due to being frequently imposed to ensure patients comply with their treatment once discharged back in the community. I found no previous research that has investigated the role of previous receipt of CTOs

or medication non-adherence on long-term antipsychotic polypharmacy prescribing.

Previous use of antipsychotic medication

Previous antipsychotic use was associated with increased risk for polypharmacy prescribing (Barbui et al. 2006; Suokas et al. 2012; Ganguly et al. 2004). Antipsychotic polypharmacy risk also increased with the number of additional antipsychotics previously prescribed [(Barbui et al. 2006)(OR=144.4; 95% CI: 31.9- 654.4)]. The risk was further sustained for both patients with chronic and recent onset schizophrenia (Suokas et al. 2012).

One meta-analysis and two large US cohort study considered the effect of clozapine prescribing in predicting long-term antipsychotic polypharmacy prescribing. Evidence from the meta-analysis indicated that there was no association (Gallego et al. 2012) between receiving clozapine and antipsychotic polypharmacy prescribing (p=0.24). Morrato et al. (Morrato et al. 2007) examined mental health claims for 55,481 patients in five US states and similarly found that clozapine was not associated with increased risk for polypharmacy (OR=1.59; 95% CI: 0.96- 2.64). However, one study also examining Medicaid insurance claims in two US states (Ganguly et al. 2004) reported that clozapine independently predicts long-term antipsychotic polypharmacy prescribing (OR=11.77; 95% CI: 9.23- 15.01; P<0.001). In the context of existing recommendations and guidelines, it is expected that clozapine would predict antipsychotic polypharmacy prescribing. However, it

is possible that the aforementioned results reflect differences in prescribing cultures across different treatment facilities and across countries

There was only one study that investigated the role of long-acting injectable (LAI) antipsychotics in polypharmacy prescribing. In their meta- analysis, Gallego and colleagues (Gallego et al. 2012) indicated that patients who have received long-acting injectable antipsychotic (LAI) were more likely to receive polypharmacy (r=0.26; p=0.04).

2.4.3 Outcomes of antipsychotic polypharmacy

Table 2.3 summarises studies extracted from Table 2.1. that have investigated mortality and readmission outcomes of long-term antipsychotic polypharmacy, in patients with SMI. The table includes information about the primary author and year, main results and confounders that were adjusted for in the analysis.

Table 2.3 Summary of literature examining outcomes of long-term antipsychotic polypharmacy prescribing.

Outcome	Study	Main Results	Confounders adjusted for
Mortality	**Baandurp et al., 2010**	The risk for natural cause of death did not increase when prescribed two or more antipsychotics, as compared to monotherapy (OR=0.91; 95%CI: 0.61-1.36).	Age and sex matched controls; further adjusted for antipsychotic medication, somatic comedication, epilepsy, benzodiazepines
	Katona et al., 2014	Monotherapy was associated with a higher risk of mortality (HR=1.62; p=0.01)(95% CI not provided) in comparison to polypharmacy.	gender, age, number of days of hospitalisation in the one year prior to the study
Readmission	**Boaz et al., 2013**	Factors associated with early readmission (first 30 days) were: Shorter hospitalisation (HR=1.18; 95% CI: 1.10-1.27) Shorter time on medication (HR=1.19; 95% CI: 1.06- 1.35) Prior substance abuse treatment (HR=1.58; 95%CI:1.37- 1.83) Antipsychotic polypharmacy was not associated with readmission (HR=1.02; 95%CI: 0.90- 1.14).	gender, ethnicity, age, days of prior acute care treatment, substance abuse treatment, presence of significant medical comorbidity, length of stay in acute care, length of time receiving discharge medication
	Katona et al., 2014	Monotherapy was associated with increased hospital readmission (HR=1.69; p<0.001)(95% CI not provided), in comparison to polypharmacy.	gender, age, number of days of hospitalisation in the one year prior to the study

Scope of previous research investigating outcomes associated with long-term antipsychotic polypharmacy prescribing

In total, I identified three studies that satisfied the inclusion criteria outlined above. Two studies considered the risk for death in patients with SMI (Katona et al. 2014; Baandrup et al. 2010), and two looked at the risk for hospital readmission following a polypharmacy prescription (Boaz et al. 2013; Katona et al. 2014).

Secondary mental health hospital readmission

Studies investigating hospital readmissions amongst patients receiving long-term antipsychotic polypharmacy have been sparse. In total, two studies examining this were identified and overall, results were mixed. Katona and colleagues (Katona et al. 2014) investigated a large cohort (n=5,480) of Hungarian insurance records and indicated that although polypharmacy was associated with more treatment discontinuation (as measured by stopping or switching antipsychotic medications; and an indicator of antipsychotic effectiveness), it was associated with lower rehospitalisation, in comparison to antipsychotic monotherapy (HR=1.69; $p<0.001$). However, Boaz and colleagues (Boaz et al. 2013) also investigated insurance records from the US state of Florida (n=3,563) and found that polypharmacy at discharge was not associated with future hospital readmissions (HR=1.02; 95% CI: 0.90- 1.14); rather readmission was associated with patients being insufficiently stable at the point of initial discharge (although the authors did not formally assess mental health stability).

Mortality

I identified two large observational studies (Baandrup et al. 2010; Katona et al. 2014) that investigated long-term antipsychotic polypharmacy prescribing and mortality. A Danish study compared 2,130 patients prescribed polypharmacy to age and sex matched patients prescribed monotherapy (Baandrup et al. 2010). The risk for natural cause of death did not increase when prescribed two or more antipsychotics, as compared to a single antipsychotic. A large Hungarian study (Katona et al. 2014) found that although antipsychotic polypharmacy had a shorter time to all-cause treatment discontinuation compared to monotherapy, monotherapy was associated with increased overall mortality in comparison to antipsychotic polypharmacy (HR=1.62; p=0.01).

2.5 Discussion

Despite considerable variation across studies, the reviewed literature indicated that factors such as younger age, single marital status, comorbid mental health diagnosis and prior service use (inpatient; outpatient and medication use) are plausible predictors of long-term antipsychotic polypharmacy prescribing in secondary mental health care. However, antipsychotic polypharmacy associations with other factors such as gender, ethnicity, employment, clinical symptoms, and specific antipsychotic treatments including clozapine and LAI remain unclear. In relation to outcomes of long-term antipsychotic polypharmacy, studies investigating mortality and hospital readmission were sparse and findings mixed. In order to draw any meaningful conclusions from the studies that have been reviewed, it is imperative to consider the findings alongside their methodological limitations.

2.5.1 General methodological limitations

Overall, a large proportion of studies investigating predictors and outcomes of antipsychotic polypharmacy have used register-based or medical insurance databases (Baandrup et al. 2010; Boaz et al. 2013; Katona et al. 2014; Ganguly et al. 2004; Morrato et al. 2007; Ortiz et al. 2016; Suokas et al. 2012). Although these studies contain data for large populations, thus increasing statistical power to detect associations, they lack contextual information, thus examining a limited number of factors and possible confounders. Confounding refers to a factor that is associated with both the exposure and outcome but does not lie on the causal pathway. On the other

hand, studies that have used information rich clinical records (Biancosino et al. 2005; Barbui et al. 2006; Moilanen et al. 2016; Santone et al. 2011) have been able to examine a wider number of factors in relation to polypharmacy. However, analysing clinical records (where researchers often read records and code it by hand according to a defined set of coding rules) is very time and labour intensive, and therefore less feasible on a large scale. This has resulted in investigating smaller and more homogeneous sample than ideal (e.g. inpatients), which limits the generalizability of findings (Biancosino et al. 2005; Barbui et al. 2006; Moilanen et al. 2016; Santone et al. 2011). Furthermore, although I classified studies that considered antipsychotic polypharmacy of 60 or more days, as long-term, these cannot definitely exclude antipsychotic cross-titration (which can take up to 10 weeks, see Chapter 1 section 1.7). Therefore, such studies may be prone to polypharmacy misclassification (Ganguly et al. 2004; Boaz et al. 2013; Katona et al. 2014; Morrato et al. 2007; Suokas et al. 2012).

2.5.2 Factor-specific methodological limitations

Age

Three large studies, two investigating clinical records (Kreyenbuhl et al. 2007; Suokas et al. 2012) and one medical insurance databases (Morrato et al. 2007) reported that younger adults are more likely to receive polypharmacy. Overall, these are good quality studies, adjusting for an array of possible confounders and encompassing large population samples, therefore increasing statistical power to detect associations. However, it is important to bear in mind that studies examining specific populations such as the Veteran

Affairs Psychosis Registry (Kreyenbuhl et al. 2007) and claims from medical health insurance (Morrato et al. 2007) may not be entirely representative of patients receiving secondary mental health care. Therefore, this could be a potential source of selection bias. Similarly, one study examining a large sample of US medical insurance claims reported an increased risk for older patients and antipsychotic polypharmacy (Ortiz et al. 2016). This study examined exclusively inpatients at discharge and therefore, may not be generalizable to patients in different treatment setting (e.g. outpatients). Three studies indicated that there is no association between age and antipsychotic polypharmacy (Santone et al. 2011; Suokas et al. 2012), including one very large meta-analysis encompassing 147 studies across the continents, with a total of over a million patients (Gallego et al. 2012). Although this study was unable to examine multiple predictors, it included research across the globe, with a sufficient power to detect possible associations. Furthermore, this finding was supported by a smaller Italian study (Santone et al. 2011) examining information-rich clinical records and a large Finnish register-based study (Suokas et al. 2012). However, it is important to highlight that the aforementioned three studies did not adjust for a number of possible confounders such as symptom severity, therefore findings are possibly subject to residual confounding. On reflection, some of the highlighted methodological limitations may partly explain some of the observed heterogeneity across evidence in this field. However, it is also possible that the above findings reflect the varying prescribing practice across facilities and countries. Further research is desirable to test the effect of age on a more generalizable population sample.

Gender

Two cross sectional studies from Italy and Finland and one large US cohort study reported that males have an increased likelihood of receiving antipsychotic polypharmacy (Santone et al. 2011; Suokas et al. 2012; Morrato et al. 2007). This is a heterogeneous group of studies investigating inpatient (Santone et al. 2011) and outpatient (Suokas et al. 2012) populations, in different countries (Italy; Finland and US), which may indicate that this finding is reasonably generalizable. However, aside from one study (Morrato et al. 2007), which adjusted for possible confounders, it is possible that the above findings are subject to residual confounding. On the other hand, two very large US medical insurance register studies (Ortiz et al. 2016; Ganguly et al. 2004); one US veteran record study (Kreyenbuhl et al. 2007) and one meta-analysis (Gallego et al. 2012) reported that gender is not associated with a risk for antipsychotic polypharmacy prescribing. Although, the latter three studies (Ortiz et al. 2016; Ganguly et al. 2004; Kreyenbuhl et al. 2007) had the advantage of adjusting for multiple potential confounders and examining larger populations, therefore having more statistical power to detect an effect, they examined specific population samples (e.g. medical insurance claims; veterans), therefore potentially reducing generalizability. Given the extensive methodological heterogeneity across the aforementioned studies, we cannot draw any definitive conclusions on whether gender predicts long-term antipsychotic polypharmacy prescribing. An important caveat worth considering here is that it is possible that prescribing cultures vary across

different countries and that differences observed across studies may in fact represent true differences across countries.

Ethnicity

Two large US cohort studies (Kreyenbuhl et al. 2007; Morrato et al. 2007) and one meta-analysis (Gallego et al. 2012) investigated the association between ethnicity and antipsychotic polypharmacy. Although Gallego et al. (Gallego et al. 2012) reported no association between white ethnicity and polypharmacy, this study did not consider any other ethnicities. Therefore, an association cannot be ruled out. Furthermore, heterogeneous classifications of ethnicity across the former two studies has made it very difficult to compare existing findings. In addition, as discussed in the previous section, although both US studies have adjusted for a number of confounders, they have focused on distinct population samples, thus comparison of findings may not be appropriate.

Marital status

One small cohort study that was unable to adjust for potential confounders reported that marital status does not predict antipsychotic polypharmacy (Biancosino et al. 2005) and two large studies from Italy and US (Santone et al. 2011; Kreyenbuhl et al. 2007), one of which (Kreyenbuhl et al. 2007) adjusted for an array of possible confounders, reported that single patients were more likely to be prescribed polypharmacy in comparison to monotherapy. It is possible that the study conducted by Biancosino et al.

(Biancosino et al. 2005) did not have sufficient statistical power to detect an effect (n=358) and may have suffered from residual confounding.

Employment/ social deprivation

In total three studies (Santone et al. 2011; Barbui et al. 2006; Biancosino et al. 2005) examined employment and antipsychotic polypharmacy. All but one (Biancosino et al. 2005) reported no association between employment and polypharmacy regimen. Although, the study by Biancosino et al. (Biancosino et al. 2005) examined the smallest population, this was a prospective study, examining an array of possible predictors from information-rich clinical records, and adjusting for a number of possible confounders. All three studies investigated inpatient populations in Italy; however Barbui et al. (Barbui et al. 2006) conducted their study across an additional three countries. The later study also specifically focused on unstable patients, therefore possibly limiting the generalizability of their findings to the wider inpatient population. In conclusion, based on this evidence it is difficult to determine whether employment in fact predicts long-term antipsychotic polypharmacy prescribing.

Comorbid diagnoses

Comorbid diagnosis such as personality disorder (Ganguly et al. 2004); depression (Kreyenbuhl et al. 2007); alcohol use (Ganguly et al. 2004), and substance use (Ganguly et al. 2004; Kreyenbuhl et al. 2007) have been associated with lower risk for long-term antipsychotic polypharmacy. One study found that substance abuse was not associated with antipsychotic

polypharmacy prescribing (Morrato et al. 2007). Both studies that investigated substance abuse, reported findings from US medical insurance records, and investigated polypharmacy of 60 or more days duration. However, records were derived from different US states, Georgia and California in Ganguly et al. (Ganguly et al. 2004) study and California, Nebraska, Oregon, Utah, and Wyoming in Morratto et al. (Morrato et al. 2007) study. Although the latter study encompassed a larger and potentially more diverse population, it is possible that differences in findings reflect differences in the populations that were examined. As previously discussed, it is likely that patients eligible for medical insurance in the US are inherently different to other non-eligible patients seen by secondary mental health services. It is also likely that eligible populations differ across states, and have different socio-demographic and clinical composition. Therefore findings need to be interpreted and compared with caution. Furthermore, despite the above studies including large patient samples and adjusting for a number of possible confounders, it is difficult to determine whether these findings are generalizable to populations across different states and outside the US. Further research is needed to replicate the results outside the US and across more diverse population samples.

Clinical symptoms

Findings regarding the role of clinical symptoms in predicting long-term antipsychotic polypharmacy prescribing have been mixed. In total, four longitudinal cohort studies investigated clinical symptoms and antipsychotic polypharmacy (Barbui et al. 2006; Gallego et al. 2012; Biancosino et al. 2005; Moilanen et al. 2016), adjusting for multiple confounders in their analysis. Two

studies reported that polypharmacy was not associated with overall or individual psychopathology symptoms (Barbui et al. 2006; Gallego et al. 2012), and two studies reported that polypharmacy was associated with positive symptoms (Biancosino et al. 2005), poor functioning, remission, and clinical outcomes (Moilanen et al. 2016). However, only two of the aforementioned studies specifically measured the clinical symptoms prior to the occurrence of antipsychotic polypharmacy (Barbui et al. 2006; Biancosino et al. 2005). Given the heterogeneity across their findings it is also important to acknowledge that the two studies focused on different clinical populations such as clinically unstable patients (Barbui et al. 2006) and inpatients (Biancosino et al. 2005). As a result, it is difficult to determine the role of clinical symptoms in predicting antipsychotic polypharmacy prescribing.

Previous service use

Existing evidence from large cohort studies consistently reported that antipsychotic polypharmacy is associated with more frequent previous hospital admissions (Kreyenbuhl et al. 2007; Gallego et al. 2012; Ganguly et al. 2004; Ortiz et al. 2016) and higher number of previous outpatient contact (Ganguly et al. 2004; Kreyenbuhl et al. 2007). The majority of this research has been conducted in the US, therefore a caveat to consider is that there has been a general paucity of research from other countries such as the UK. As a result, findings need to be generalised to other populations with caution.

Although studies conducted to date indicate that the number of previous antipsychotic drugs is associated with increased risk for polypharmacy (Barbui

et al. 2006; Suokas et al. 2012; Ganguly et al. 2004), evidence regarding the use of individual antipsychotics such as clozapine has been mixed. Three studies investigated clozapine use and antipsychotic polypharmacy (Gallego et al. 2012; Ganguly et al. 2004; Morrato et al. 2007); however only one (Morrato et al. 2007) examined clozapine as a predictor of polypharmacy, thus specifying that clozapine prescription had to occur prior to polypharmacy. Therefore, at present it is difficult to determine whether clozapine prescribing predicts long-term antipsychotic polypharmacy. Furthermore, out of the literature that qualified for this review, only one reported findings on long-acting injectable (LAI) antipsychotics (Gallego et al. 2012), although they were unable to distinguish between this factor being a characteristic or a predictor of antipsychotic polypharmacy. Therefore, it is difficult to determine whether LAI predicts antipsychotic polypharmacy prescription.

An important caveat to consider in relation to the aforementioned research is that existing studies have also sporadically investigated the effect of previous antipsychotic polypharmacy episodes on the risk for future antipsychotic polypharmacy prescribing (Barbui et al. 2006). More specifically, it is possible that previous antipsychotic polypharmacy episodes influence future service use, therefore studies that have not examined initiation of antipsychotic polypharmacy, may interpret factors as predictors of polypharmacy, where in fact they could be consequences of past polypharmacy episodes. This could be a potential source of reversed causality.

Mortality and readmission

In total two studies investigated hospital readmission (Boaz et al. 2013; Katona et al. 2014) and two studies investigated mortality (Baandrup et al. 2010; Katona et al. 2014) in relation to long-term antipsychotic polypharmacy prescribing. There were several important methodological consideration that need to be accounted for in view of the heterogeneity of the findings discussed in the Results section of this chapter.

Two out of the three studies (Katona et al. 2014; Boaz et al. 2013) included exclusively information on populations eligible for medical insurance. As discussed in the previous section, it is possible that such samples do not provide a true reflection of patients with SMI seen by secondary mental health care. Therefore, their results need to be generalised with caution. Lastly, as a result of investigating database (Baandrup et al. 2010) and insurance records (Katona et al. 2014; Boaz et al. 2013), which often contain limited contextual information, which might be used as a source of potential confounders in multivariable models, it is possible that the above results are subject to residual confounding. More specifically, an important confounder that has not been considered by any of the aforementioned studies is antipsychotic dose. Approximately 20% of UK patients (Paton et al. 2008; Harrington 2002) and 28% internationally (Barbui et al. 2006) are prescribed high doses of antipsychotics. High-dose prescribing is especially prevalent in inpatient settings [estimated at around 55% (Grech & Taylor 2012)], where prevalence of polypharmacy is also high. In fact, existing research suggests that high dose prescribing is often associated with antipsychotic polypharmacy in both

inpatients and outpatients (Barnes & Paton 2011a; Barbui et al. 2006; Paton et al. 2008; Tungaraza et al. 2010), with PRN medication significantly contributing to this (Paton et al. 2008; Milton et al. 1998; Harrington 2002). High dose antipsychotic regimens have been associated with a considerable side-effect burden such as increased risk for extra-pyramidal side effects (Centorrino et al. 2004), hyperprolactinemia; QTc prolongation and sedation (Auquier et al. 2006; Raedler 2010; Suzuki et al. 2014). Another factor that has been generally poorly adjusted for, and not accounted for by the aforementioned studies, is smoking, which is especially prevalent amongst patients with SMI (Brown et al. 2000) and has a well established detrimental effect on physical health and mortality (Goff et al. 2005; Brown & Mitchell 2012).

Mortality studies that have not been included

There were several important studies that could not be included in this review because they did not specify the duration of antipsychotic polypharmacy that was examined. Therefore, it is very likely that those studies included cases of both short and long-term antipsychotic polypharmacy.

Three cohort studies investigating mortality in patients with SMI reported that the use of antipsychotic polypharmacy is associated with increased risk for overall death (Kiviniemi et al. 2013; Joukama et al. 2006; Waddington et al. 1998). The first of these, a large Finnish study, also reported an association between death from suicide and FGA-only polypharmacy, and SGA-only polypharmacy, in comparison to patients not taking antipsychotics.

Furthermore, the same study reported that cardiovascular death was also associated with FGA-only polypharmacy. Although, this was a large cohort study, that was representative of the population it examined, the analysis was not adjusted for factors such as antipsychotic dose, thus potentially suffering from residual confounding. Similarly, Joukamma et al. (Joukama et al. 2006), also a large, representative Finnish study, adjusted for a multitude of socio-demographic, socioeconomic, physical health and lifestyle factors; however, they did not control for the effect of antipsychotic dose. Waddington et al. (Waddington et al. 1998) examined 88 inpatients in Ireland. Although the study reported descriptive information about antipsychotic dose, they did not include it as a covariate in the Cox analysis. Aside from the first study (Kiviniemi et al. 2013), both Waddington et al. (Waddington et al. 1998) and Joukamma (Joukama et al. 2006) have examined small and homogeneous patient samples, therefore potentially reducing the generalizability of their findings.

Only one of the studies that was not included in this review reported no association between death and antipsychotic polypharmacy as compared to antipsychotic monotherapy (Tiihonen et al. 2012). This was a large Finnish study using a linked national database. However, this study was unable to examine inpatients, due to no access to inpatient records, therefore findings are only representative of the Finnish outpatient population. Furthermore, similarly to the studies above, dose was not included as a covariate in calculating the risk of death, therefore results are potentially subject to residual confounding.

2.5.3 Conclusion

This review of literature on predictors and outcomes of long-term antipsychotic polypharmacy prescribing revealed several important findings. Although there has been considerable previous research that has investigated factors that characterise and predict antipsychotic polypharmacy, previous studies have been limited by investigating a limited number of factors in the same study, mostly due to unavailability of diverse contextual information. Therefore, findings on different predictors have been derived mainly from studies using different methodologies and populations samples. In addition, the aforementioned research has investigated a limited number of potential confounders, thus risking residual confounding. Furthermore, although there have been some large cohort studies, generalizability of findings has been difficult beyond the populations that were examined, due to samples focusing on specific population groups (e.g. inpatients; medical insurance claimants). Therefore it remains unclear whether key patient factors such as gender, ethnicity, social deprivation and clinical symptoms, predict antipsychotic polypharmacy prescribing in other patient populations. Despite the above limitations, this review provided some support for the hypothesis that factors such as previous inpatient and outpatient use predict the prescribing of long-term antipsychotic polypharmacy.

In relation to outcomes of antipsychotic polypharmacy, a large proportion of studies investigating polypharmacy and mortality did not qualify for this review, as a result of not specifying the duration of the concomitant antipsychotic use that was investigated. Consequently, only three studies

could be reviewed in detail. Overall, studies were limited by investigating relatively small samples and possible residual confounding, due to not adjusting for key factors such as antipsychotic dose and smoking. As a result, it is difficult to determine whether antipsychotic polypharmacy is associated with a change in the risk of death and hospital readmission.

There has been an extensive number of studies coming from US, Italy and Finland. However, there has been a considerable paucity of evidence from UK based studies. Therefore, it remains unclear whether the above findings can be generalised to the UK population. Although general guidelines, especially concerning antipsychotic polypharmacy, are similar across countries (e.g. APA and NICE), it is possible that different countries differ in their medication prescribing culture (Howes et al. 2012).

In conclusion, there is a clear need for large cohort studies that are representative of the population seen by secondary mental health care, and that have access to diverse contextual information. The above will ensure that the studies are: 1) able to simultaneously measure a diverse number of possible predictors and outcomes in the same sample of patients; 2) measure a range of possible confounders, and thus test the robustness of the findings; 3) have sufficient power to detect an association with rare outcomes such as death; 4) have sufficient statistical power to adjust for multiple confounders simultaneously in the analysis; 5) provide findings which are generalizable across a diverse range of patients (e.g. inpatients and outpatients). Furthermore, there is a clear need for UK-based research that examines

possible predictors and outcomes in NHS settings. Lastly, there is a clear need for a better method of identifying long-term antipsychotic polypharmacy prescribing on a large scale. This type of concurrent antipsychotic administration can be difficult to detect in contrast to its other subtypes with more transient nature (i.e. PRN medication; cross-titration). Smaller studies that have manually examined clinical records have been better at specifying and identifying long-term antipsychotic polypharmacy. However, this latter process is very time and labour intensive and not possible on large scale. Therefore, there is a need to develop a method that can detect polypharmacy fast, on a large scale, and which has the potential to be used across different datasets with a similar set-up.

CHAPTER 3: THESIS RATIONALE AND OBJECTIVES

3.1 Overall thesis objectives:

1) To identify cases of long-term (≥ 6 months) antipsychotic polypharmacy prescribing in South London and Maudsley electronic health records (EHR).

2) To identify factors that predict long-term antipsychotic polypharmacy prescribing for SMI patients in secondary mental health care.

3) To investigate whether outcomes including hospital readmission and mortality are associated with long-term antipsychotic polypharmacy prescribing in secondary mental health care.

3.2 Study-specific rationale and aims:

3.2.1 Chapter 5: Developing and evaluating a novel process of extracting antipsychotic polypharmacy data from electronic health records.

Few existing studies have been able to distinguish between regular long-term antipsychotic polypharmacy prescribing and polypharmacy resulting from cross-titration or PRN medication administration (see Chapter 2 Table 2.1). Furthermore, existing evidence is mainly derived from studies using prescription databases (Boaz et al. 2013; Ganguly et al. 2004; Ortiz et al. 2016; Katona et al. 2014), which have only limited contextual information. In contrast, EHRs contain large volumes of detailed information in free text and

structured fields, providing an important resource for conducting analyses using large samples, and investigating a multitude of patient characteristics and adjusting for a broad range of potential confounders.

Aim: To develop, test and implement a novel algorithm for detecting long-term antipsychotic polypharmacy prescribing in secondary mental health care, through the use of electronic health records.

3.2.2 Chapter 6: Predictors of long-term antipsychotic polypharmacy prescribing in secondary mental health care.

Existing research examining predictors of long-term antipsychotic polypharmacy has been hampered by limited generalizability due to examining small and selective samples (Centorrino et al. 2005; Centorrino et al. 2004), limited number of predictors (see Chapter 2), and limited ability to distinguish temporally between the occurrence of polypharmacy prescribing and that of exposures, which has made it difficult to determine if the latter are predictors or consequences of polypharmacy (Suokas et al. 2012; Santone et al. 2011; Ortiz et al. 2016).

Aim: To investigate socio-demographic, socioeconomic, clinical, and service-use predictors of long-term antipsychotic polypharmacy initiation in a population with serious mental illnesses, in secondary mental health care.

3.2.3 Chapter 7: Antipsychotic polypharmacy prescribing and risk of hospital readmission in secondary mental health care.

Antipsychotic polypharmacy prescribing has not been found to be associated with more clinical improvement at the point of inpatient discharge, in comparison to monotherapy (Centorrino et al. 2005; Centorrino et al. 2004; Biancosino et al. 2005). However, despite the lack of evidence to support its effectiveness, the prescribing of antipsychotic polypharmacy has persisted across clinical services and over time (Gallego et al. 2012; Correll & Gallego 2012; Paton et al. 2008). At present, the evidence on the effectiveness of this regimen, once patients return to the community, is sparse and mixed, with studies reporting an association with both reduced and increased risk for hospital readmission (see Chapter 2 Table 2.3). However, research has indicated a modest benefit for clozapine co-prescribing in relation to outcomes such as readmission (Freudenreich & Goff 2002; Taylor et al. 2011).

Aim: To investigate whether receiving an antipsychotic polypharmacy prescription at the point of inpatient discharge is associated with future hospital readmissions into secondary mental health care. In addition, I investigated whether receiving clozapine as part of the polypharmacy regimen had an effect on this risk.

3.2.4 Chapter 8: Long-term antipsychotic polypharmacy prescribing in secondary mental health care and the risk of mortality.

To date, it has been widely believed that antipsychotic polypharmacy increases the risk for detrimental health outcomes such as mortality (Waddington et al. 1998; Joukama et al. 2006; Kiviniemi et al. 2013). However, on closer inspection, research investigating the effect of long-term antipsychotic polypharmacy has been extremely sparse (see Chapter 2 Table

2.3). Findings have been primarily derived from small studies, examining antipsychotic polypharmacy of unspecified duration, and therefore are likely to have included long-term polypharmacy as well as PRN medication and antipsychotic cross-titration. Furthermore, the effects of factors such as antipsychotic dose have been inconsistently investigated (see Chapter 2 section 2.5.2), thus findings are subject to potential residual confounding. Consequently, it is difficult to known whether the observed associations are in fact due to antipsychotic polypharmacy prescribing.

Aim: To determine whether long-term prescribing of antipsychotic polypharmacy has an effect on the risk of death in patients with serious mental illness receiving treatment in South London and Maudsley mental health services. Furthermore, I set out to investigate whether this risk varied depending on the cause of death and other factors such as antipsychotic dose.

CHAPTER 4: METHODS

The contents of this chapter have contributed to the following:

Publications in peer-reviewed journals

Perera, G., Broadbent, M., Callard, F., Chang, C.-K., Downs, J., Dutta, R., Fernanades, A., Hayes, RD., Henderson, M., Jackson, R., Jewell, A., **Kadra, G**., Little, R., Pritchard, M., Shetty, H., Tulloch, A. & Stewart, R. (2016). Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. *BMJ Open* , *6* (3). doi:10.1136/bmjopen-2015-008721

4.1 Overview

Data used in the analyses described in Chapters 5,6,7,8 were derived from the Clinical Record Interactive Search (CRIS) data resource, developed within the NIHR Mental Health Biomedical Research Centre and Dementia Unit (BRC/U), which allows researchers to search and retrieve de-identified clinical data sourced from the SLAM EHRs. CRIS is a dynamic database, which updates against source files every 24 hours. At the time of writing, it contains more than 280,000 cases.

In this chapter I describe the study settings, the operational model of the CRIS interactive search tool, and the main exposure of interest. In addition, I provide a brief overview of the main statistical analyses that will be used in further individual chapters.

4.2 Setting

SLAM is one of the largest providers of secondary health care in the UK, serving a geographic catchment of 1.23 million residents across four London boroughs (Lambeth, Southwark, Lewisham and Croydon) (Stewart et al 2009), which is representative of the population seen by the National Health Services in South East London. In addition, the Trust also provides care for some regional/national patients in specialist services. Overall, there are seven specialty groupings: Addictions; Behavioural and Developmental Psychiatry; Child and Adolescent Mental Health Services; Mental Health of Older Adults and Dementia; Mood, Anxiety and Personality; Psychological Medicine; Psychosis.

4.3 Data source

4.3.1 Electronic Health Records

EHRs have been kept by SLAM across all services since 2006, using the Patient Journey System (see below). SLAM EHRs contain a large volume of diverse data, thus making it possible to examine a multitude of factors and simultaneously control for a range of potential confounders in analyses. Furthermore, the above also makes it possible to examine outcomes that occur less frequently, such as death. In addition, the data are longitudinal, allowing for factors to be measured at multiple points, so that temporal relationships between measured factors can be determined. Moreover, findings are reflective of real-world clinical practice.

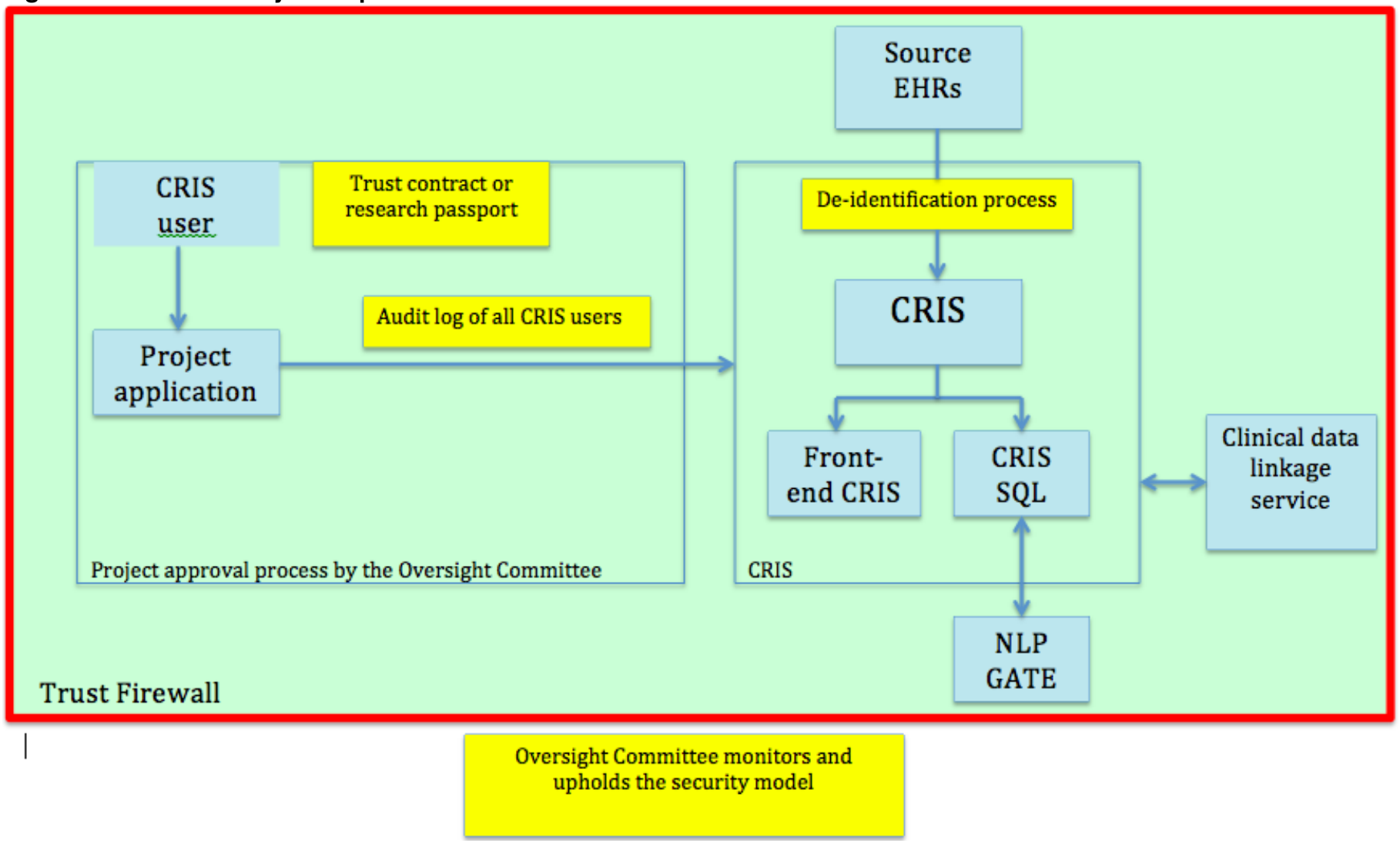
4.3.2 The Patient Journey System

The Patient Journey System (PJS) was developed between October 2005 and October 2006 to integrate paper and EHRs across all services in SLAM, thus facilitating the recording and sharing of clinical information within and across multidisciplinary teams. PJS contains a comprehensive record of patient's demographics, contact information, referrals, transfers, detailed clinical assessments, care plans, medication, clinical activity and reviews. Information is organized in structured fields (such as dates and drop down menus) and unstructured free text (including written assessments, progress notes and correspondence)(Stewart et al. 2009).

4.3.3 Clinical Record Interactive Search (CRIS)

In 2008 the CRIS system was developed, which allows researchers to search and retrieve de-identified SLAM EHR data. CRIS currently accesses over 280,000 cases. Patients are able to opt out from CRIS; however to date only three people have done so. Ethical approval as an anonymised database for secondary analysis was originally granted in 2008, and renewed for a further 5 years in 2013 (Oxford C Research Ethics Committee, reference 08/H0606/71+5). Figure 4.1 illustrates the CRIS security and operational model. The figure has been adapted from Fernandes et al. (Fernandes et al. 2013) and Perera et al. (Perera et al. 2016).

Figure 4.1 CRIS security and operational model.



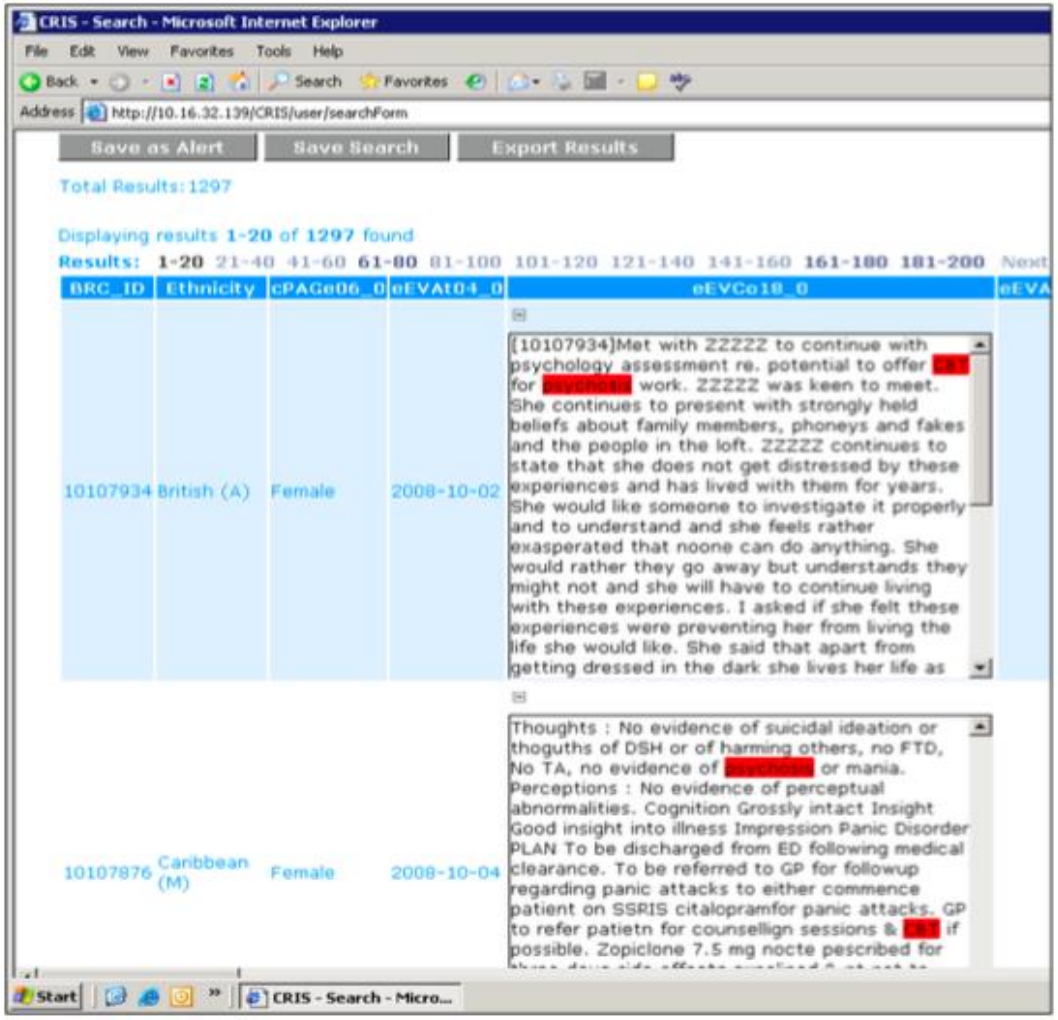
The CRIS security model was developed and is managed by an Oversight Committee, which is chaired by a mental health service user; a SLAM BRC Stakeholder; a SLAM Research Ethics Committee representative; a SLAM Caldicott Guardian representative; a Child and Adolescent Mental Health representative; a CRIS Academic Lead; and a CRIS Project Manager. The Committee was formed to uphold and monitor CRIS security. In addition, the Committee is responsible for considering and approving potential CRIS project applications. In order for an applicant to be able to work with CRIS they require the following: a SLAM audit committee approval; a senior university or NHS affiliated supervisor attached to and taking responsibility for the project and the applicant; a formal affiliation (either honorary or substantive) with the hospital or the university (this ensures that the applicant is bound by NHS duty of confidentiality); to complete a Project Approval Form (where they are asked to describe the purpose of the proposed project and the nature of the data required for analysis) and obtain an approval from the Oversight Committee (Fernandes et al. 2013). All applications are considered carefully in relation to their scientific robustness and patient confidentiality (for example, research projects examining small patient samples with rare conditions, may pose risk regarding patient anonymity, therefore may not be approved)(Fernandes et al. 2013). If an approval is granted, the researcher is able to access CRIS within the SLAM firewall. All projects are audited weekly to ensure they adhere to the project approval.

CRIS de-identifies PJS records by identifying, marking and masking patient identifiers with ZZZZZZ (and carer identifiers with QQQQQQ), thus facilitating

the use of clinical data for research purposes. Figure 4.2 illustrates how this appears in Front-End CRIS (see section 4.4.1). This figure has previously been published by Stewart et al. (Stewart et al. 2009). Due to confidentiality, I could not use a snapshot from my work. The bespoke de-identification algorithm was developed by the team and its performance evaluated using 500 patient notes (Fernandes et al. 2013). The algorithm achieved 98.8% precision (the proportion of personal identifiers that were correctly de-identified, out of all those that were de-identified by the algorithm) and 97.6% recall (the number of personal identifiers the algorithm de-identified out of all the personal identifiers in the text). In addition the performance of the algorithm was also compared to a Machine learning Identification Scrubber Toolkit (MIST) (Aberdeen et al. 2010). In total 70 patient notes were investigated and the performance test indicated a superior precision and recall using the CRIS algorithm: precision 100% (CRIS) versus 95.6% (MIST) and recall 88.5% versus 78.1%, respectively. Although breaches in data are possible and did occur, they were very rare. In the above evaluation study, 1 patient note out of 500 that were examined, was a potential breach (which was defined as having three or more instances of potential personal identifiers). The authors (Fernandes et al. 2013) concluded that even in such instances the information and identity of the patient cannot be established by the researcher. In addition, the researcher, who is also bound by the duty of confidentiality, would need to be actively trying to identify the patient in order to breach confidentiality. Furthermore, in order to minimize patient identification, some personal information has been truncated. For example

only the first half of postcodes and only the month and year of birth are included in CRIS (Stewart et al. 2009).

Figure 4.2 Screenshot of Front-End CRIS results with de-identified patient information.



CRIS provides longitudinal information, which updates against source files every 24 hours (Perera et al. 2016). This allows researchers to examine dynamic cohorts, which not only have extensive historical data, but in addition could have new clinical information coming in. Data are available from both structured and unstructured fields from PJS. Structured data refers to information that is recorded as dates and in drop-down menu fields. It represents single entities such as ethnicity, marital status and employment. In addition, researchers can access routinely collected data resources such as the Health of the Nation Outcome Scale (HoNOS). Although none of the fields used in this thesis (see Table 4.2 below) require compulsory completion by clinicians, socio-demographic information tends to have a better completion rate than information such as clinical rating scales (e.g. HoNOS). This is further discussed below in section 4.8. However, it is important to highlight that there has been a variation on information completeness over the years, especially when considering clinical scales, with a trend towards higher completion rate in more recent years. However, in many cases clinical scales may be completed only once and not repeated in the observation period under investigation. Unstructured data refers to information available in free text fields such as clinical notes, correspondence and inpatients events. Although completion rate of free text is discretionary to staff, in the NHS clinicians are required to record every contact (e.g. telephone calls; face-to-face meetings, paper and email correspondence) that they have with patients. However, the timely manner in which this is achieved can vary across clinicians and services.

4.4 Data extraction from CRIS

4.4.1 Front-End CRIS

Front-End CRIS allows researchers to view a de-identified version of PJS and search against any combination of structured (e.g. dates; diagnosis) and unstructured (e.g. progress notes, correspondence) fields. The system returns relevant 'hits' (i.e. records) based on entered search terms (see Figure 4.2). Results are collated in a spread sheet format and can be exported as CSV files for further analysis (Perera et al. 2016). In the context of my project, Front-End CRIS was used to manually validate information on antipsychotic polypharmacy cases and dose as described in Chapter 5 section 5.3.5 and Chapter 8 section 8.3.5, respectively.

4.4.2 Structured Query Language (SQL)

SQL is programming language designed to manage data from multiple sources. This approach allows researchers to combine information available from structured and unstructured fields in CRIS by writing queries and retrieving data for a specific cohort. Results are displayed as tables for researchers to allow manual coding of data. One of the advantages of this method is that it also allows researchers to devise further filters after examining the data. For example, in this project, to improve the identification of antipsychotic polypharmacy, following a manual examination of the data, I further applied filtering criteria to the data extraction to improve the precision and recall of the output data (as will be described in Chapter 5, section 5.3.5).

4.4.3 Natural Language Processing (NLP)

In CRIS, specific NLP algorithms are available, which extract and code pharmacotherapy data from free-text fields, taking into account the linguistic context in which keywords appear. As opposed to simple keyword search, the application is able to distinguish between instances of antipsychotic prescription, which apply to the patient in question, as opposed to medication that has been prescribed for a family member, for example.

The validity of the NLP applications has previously been evaluated in relation to diagnosis, smoking and antipsychotic medication. The smoking application (Wu et al. 2013; Perera et al. 2016) was developed by extracting information from unstructured fields on whether patients were either currently smoking, have smoked in the past, or have never smoked [smoking of substances other than tobacco (e.g., marijuana/cannabis and cocaine) were excluded]. The application was developed through an iterative process where a manual 'gold standard' annotation of documents consisting of unstructured fields were compared to the results generated by the application. The final application was tested on clinical notes of 100 patients, yielding a precision of 0.93 and 0.58 recall. To test the diagnosis application, any available text strings associated with a diagnosis statement were identified from free text. This information was designed to supplement information already available through the existing structured (International Classification of Diseases (ICD)-10) fields. The performance of the application was evaluated in a random sample

of 75 documents for ‘vascular dementia’, indicating 0.99 precision and 0.98 recall (Sultana et al. 2014). The antipsychotic medication application was developed using a gazetteer of generic and commercial names for all medications in UK use. The application was first tested on clozapine use, investigating both current use of clozapine (precision 0.96; recall 0.92) and both past and present (ever) use (precision 0.99; recall 0.98). The evaluation for precision was based on comparing the performance of the application against a manual search of 279 documents. Recall was evaluated on a random set of 200 documents containing the word clozapine (Hayes et al. 2014). In Chapter 5, I describe the validity of the application on antipsychotic polypharmacy.

General Architecture for Text Engineering (GATE) software (Cunningham et al. 2013; Cunningham 2002) is a suite of tools that allows NLP applications to be built. It allows for a variety of text processing tools and document formats to be used, with individual tools being chained together into processing ‘pipelines’, and documents processed in series through these pipelines (Perera et al. 2016). The GATE application used in this study was designed to extract antipsychotic prescription information data from free text, such as drug name, information on dose, frequency, the status of the prescription (start, stop, continuing) and the date and the relative nature of the prescription (current, in the past, or planned for the future). The full technical workings of the GATE application are beyond the scope of this project; however, they are available in this article (Cunningham 2002). GATE use for data extraction on antipsychotic polypharmacy is described in Chapter 5 section 5.3.3.

4.4.4 CRIS linkage with other databases

CRIS has been linked to other national databases, such as Primary Care, Hospital Episode Statistics, Department of Education National Pupil Database, Cancer, and Mortality (from the Office of National Statistics). In this thesis I have focused on data linkage with Office of National Statistics (ONS) mortality data, which includes information available on patients' death certificates, such as cause of death. Although, CRIS contains basic mortality information such as date of death, available through standard linkage with SLAM NHS numbers, it does not contain information such as causes of death (Perera et al. 2016). To achieve this linkage, anonymised BRC IDs are linked to the ONS death register using the Clinical Data Linkage Service (see Figure 4.1). More specifically, the Clinical Data Linkage Service sends identifiers (CRIS ID, first name, last name, date of birth, gender, postcode and NHS number) to the Health and Social Care Information Centre, who in turn request the mortality data from the ONS, and then return the mortality data to the Clinical Data Linkage Service via a secure file transfer protocol. In addition to securely linking and extracting data, the Clinical Data Linkage Service is also responsible for storing the data in accordance with the SLAM ICT Security Policy on a server within the SLAM firewall (Perera et al. 2016).

4.5 Personal contribution to data extraction

I am the first researcher to examine antipsychotic polypharmacy using the CRIS database. I was jointly responsible (with my supervisors) for designing the studies. Data extraction was completed in collaboration with the clinical

informaticians in the CRIS team; however, I provided detailed instructions on the selection parameters, specifying individual variables, coding and time frames. Furthermore, I developed a novel algorithm and devised a number of data extraction filters to derive information about polypharmacy (see Chapter 5). This involved searching for empirical research and manual examination/ validation of clinical records through Front-End CRIS (see Chapter 5 section 5.3.5 and Chapter 8 section 8.3.5 for a detailed description of the validation process). In addition, I conducted all the data analyses, wrote manuscripts (in collaboration with my supervisors and co-authors), submitted and published my research in peer-reviewed journals.

4.6 Studies selection criteria

For each of the analyses described in Chapters 5,6,7 and 8, I identified all patients who had received a SMI diagnosis, were aged 16 years or over and were active in SLAM clinical services during the observation period. Study specific observation periods are defined within each chapter. Active in SLAM service was defined as having an open team episode in PJS, in other words, there was an on-going contact between the patient and a team within the service (for each project this has been specified in the respective chapter). SMI was defined as having received a schizophrenia (ICD-10 code: F20.x), schizoaffective disorder (F25.x) or bipolar disorder (F31.x) diagnosis in the study observation window. The SMI term is used to group diagnoses of psychotic disorders such as schizophrenia, schizoaffective disorder and bipolar affective disorder. Clinical symptoms are believed to lie on a continuum between these diagnoses and it is not uncommon that a diagnosis

is changed over the course of the patient's illness (Esterberg & Compton, 2009). A decision to include all three of the above diagnoses was made based on discussions with clinicians within the BRC and previous published literature. More specifically, previous research from SLAM (Grech & Taylor, 2012) has indicated that a proportion of patients prescribed long-term antipsychotic polypharmacy have a bipolar affective disorder diagnosis. In addition there are several other UK and international studies examining physical and mortality outcomes in relation to antipsychotic polypharmacy, who have similarly indicated that this antipsychotic regimen is common amongst patients diagnosed with bipolar disorder (Osborn et al. 2014; Laursen et al. 2014; Morrato et al. 2007). Diagnostic data were derived from diagnostic structured fields within CRIS and supplemented by information available from free text, as discussed in this chapter.

4.7 Main exposure variables

Antipsychotic polypharmacy was the main exposure for all studies (Chapter 7 and 8) apart from the study in Chapter 6, which aimed to identify predictors of long-term antipsychotic polypharmacy. Long-term antipsychotic polypharmacy was defined as the concomitant prescription of two or more antipsychotics for six or more months (see also Chapter 5 section 5.3.4). Previous research has examined antipsychotic polypharmacy of varying duration (Broekema et al. 2007; Clark et al. 2002; Faries et al. 2005; Ganguly et al. 2004; Ito et al. 2005; Jaffe & Levine 2003; Janssen et al. 2005). Based on evidence presented in Chapter 1 and 2, I concluded that research that has investigate antipsychotic polypharmacy with a duration of 70 days or less cannot definitively exclude

switching (Barbui et al. 2006; Ganguly et al. 2004; Kreyenbuhl et al. 2007; Morrato et al. 2007), which can take up to 10 weeks to complete (Correll et al. 2011; Lochmann van Bennekom et al. 2013). Therefore, following consultations with psychiatrists and pharmacists working in SLAM and the BRC, I decided that antipsychotic polypharmacy of six or more months was most likely to minimise the possibility of misclassifying brief periods of antipsychotic co-prescribing, such as switching and PRN medications, as regular long-term polypharmacy; although this approach cannot absolutely exclude cross-titration that has taken unusually long (see Chapter 1 section 1.7). Antipsychotic monotherapy was defined as a patient receiving a prescription for a single antipsychotic medication listed in the BNF (British National Formulary 2015), see Table 4.1. Antipsychotic agents were further categorised as either FGA or SGA, to enable me to explore profiles of antipsychotic administration. Medication data were extracted from the SLAM pharmacy-dispensing database, and from structured and free-text fields in CRIS. SLAM pharmacy-dispensing database mostly reflects medications dispensed on the inpatient wards. However, at present some medications such as clozapine are better recorded than others. This information is available in CRIS as a structured field. Chapter 5 describes in detail the data-extraction process. Briefly, structured fields record specific antipsychotics that have been prescribed. Although these fields are expected to be regularly completed, upon manual examination, I established that the majority of medication information is provided in the free-text fields. Therefore, structured information on antipsychotic medications was supplemented by information derived from free text, using the NLP application, described above in section

4.4.3. Overall precision and recall of extracting antipsychotic medication data is discussed in detail in Chapter 5 section 5.3.5 and Chapter 8 section 8.3.5. However, below I outline how the validation of antipsychotic medications and its dose was carried out.

Table 4.1 Antipsychotic medications.

Antipsychotic name (brand name)
Amisulpride (*Solian®*)
Aripiprazole (*Abilify®*)
Asenapine *(Sycrest®)*
Benperidol
Chlorpromazine (*Largactil®*)
Clozapine (*Clozaril®, Denzapine®, Zaponex®*)
Flupentixol (*Fluanxol®, Depixol®*)
Fluphenazine *(Modecate®)*
Haloperidol (*Dozic®, Haldol®, Serenace®*)
Levomepromazine (*Nozinan®*)
Olanzapine (*Zyprexa®, ZypAdhera®*)
Paliperidone (*Invega®, Xeplion®)*
Pericyazine
Perphenazine (*Fentazin®*)
Pimozide (*Orap®*)
Pipothiazine *(Piportil®)*
Prochlorperazine
Quetiapine (*Seroquel®, Seroquel XL®*)
Risperidone (*Risperdal®, Risperdal Consta®)*
Sulpiride (*Sulpor®, Dolmatil®*)
Trifluoperazine (*Stelazine®*)
Ziprasidone
Zuclopenthixol (*Clopixol®*)

4.7.1 Validation process

The validation of the antipsychotic polypharmacy algorithm that was developed as part of this thesis is described in detail in Chapter 5 section 5.3.5. In this section, I outline the general framework that was used to re-validate the algorithm, for the study discussed in Chapter 8, and also used to validate antipsychotic dose (Chapter 8). To establish precision (positive predictive value), I selected a number (specific information on the number of patients selected to validate antipsychotic medication and dose is described in Chapter 8 section 8.3.5) of random cases identified as taking antipsychotic polypharmacy in my cohort. This was achieved using a random number generator (www.random.org). Using Front-End CRIS (see section 4.4.1 of this chapter) I manually coded the patients' clinical notes to establish whether the number of antipsychotics concomitantly prescribed and/or dose were correct in my data extraction. The index date of the antipsychotic regimen (see Chapter 8 section 8.3.4) was used as the start point for the search of clinical records, to ascertain whether the patient had been in fact prescribed the regimen for at least six months. Sources of information that I examined in Front-End CRIS were structured fields related to medication and pharmacy dispensation; in addition I examined two sources of free-text information (Ward progress notes and Correspondence). This manual examination established the 'true' occurrence of the antipsychotic regimen. The manually derived information was then compared to the information I had in my dataset, to establish precision. Match for antipsychotic polypharmacy was defined as the patient 'currently' (at the time of the document) receiving two or more antipsychotics in the documents available through Front-End CRIS. Common

mismatches included antipsychotics that have been prescribed in the past and antipsychotics that were cross-titrated. The same principle was applied to validating antipsychotic monotherapy.

To establish the total antipsychotic dose that was prescribed, I needed the following information: dose value (e.g. 15), dose unit (e.g. mg) and dose frequency (e.g. once a day). I generated a number of different rules based on specific assumptions, in order to be able to calculate the total prescribed dose, in cases where there was some missing information (the performance of all these assumptions was also validated prior to their application in the final validation). At the data extraction point, if a dose value was missing, within six weeks of the index date of the antipsychotic, then antipsychotic dose could not be calculated. At the post-processing stage, when total dose was calculated, if a dose unit was missing, then antipsychotic dose could not be calculated; if the dose frequency was missing, I assumed the medication was to be taken ‘once a day’. To establish antipsychotic dose precision, I used the same principle of checking the total dose from my dataset against documents in Front-End CRIS (using the index date as the reference point). Matches were defined as having the same dose value, unit and frequency (if available) in the extracted dataset as in the source record in Front-End CRIS. Common mismatches for dose included clinical suggestions to change antipsychotic dose that were not actually implemented; and detecting past antipsychotic doses.

To estimate recall (sensitivity), I selected a random subset of individuals from my dataset, irrespective of their antipsychotic regimen (no medication, antipsychotic monotherapy or polypharmacy) and manually coded their clinical notes for the periods that they were active in SLAM services (between 1st January 2007 and 31st December 2014), using Front-End CRIS, to determine whether they were identified correctly, with respect to antipsychotic medication use.

4.8 Covariates

Table 4.2 describes socio-demographic, socioeconomic, clinical and service use covariates used in the different chapters of this thesis. Below I outline the source of these covariates from PJS and how well they have been populated. However for specific project timings please refer to individual chapter sections (see Chapter 6 section 6.3.3; Chapter 7 section 7.3.3; Chapter 8 section 8.3.7). Although clinical staff are advised to complete as much patient information as possible, none of the factors discussed below are compulsory fields within PJS. Furthermore, over the years categories and groupings may have changed, such as for example, ethnicity has been expanded, including a larger choice of options. Other information such as clinical checklists (e.g. HoNOS see below) have been better completed in recent years, as compared to 2007 and 2008.

Table 4.2 Classification of socio-demographic, socioeconomic, clinical and service use covariates for Chapters 6,7 and 8.

Variables (% data completed)	Chapter 6	Chapter 7	Chapter 8
Age (99.7)	Categorical (16-35; 36-45; 46- 55; 56+)	Continuous	Continuous
Gender (100%)	Categorical (male / female)	Categorical (male / female)	Categorical (male / female)
Ethnicity group (98.65%)	Categorical (White; Black Caribbean; Black African; Other)	Categorical (British; Other White; Asian; Black Caribbean; Black African; Other)	Categorical (British; Other White; Asian; Black Caribbean; Black African; Other)
Relationship status (93.48%)	Categorical (no relationship; in a relationship)	Categorical (no relationship; in a relationship)	Categorical (no relationship; in a relationship)
Employment (40.49%)	Categorical (in paid employment; not in paid employment)	Not included	Categorical (in paid employment; not in paid employment)
Deprivation level in area of residence (98.5%)	Categorical (low level; medium level; high level and homelessness)	Categorical (low level; medium level; high level and homelessness)	Categorical (low level; medium level; high level and homelessness)
HoNOS (84.46%)	Six items included:	Nine items included:	Not included

	Overactive and aggressive behaviour Non accidental self-injury Cognitive problems Physical illness or disability Hallucinations or delusions Problems of activities of daily living	Overactive and aggressive behaviour Depressed mood Non-accidental self-injury Physical illness or disability Hallucinations or delusions Problems of activities of daily living Problems with living conditions Problems with occupations Problems with relationships	
Comorbid Diagnosis	ICD-10 Code: F32, F33 (Depression) ICD-10 Code: F10-16 (Alcohol and substance use) ICD-10 Code: F60; F61 (Personality Disorder)	ICD Code 10: F10 (Alcohol Use) ICD Code 10: F11 (Opioid use)	ICD-10 Code: F32, F33 (Depression) ICD-10 Code: F10-16 (Alcohol and substance use) ICD-10 Code: F60; F61 (Personality Disorder)
Days of inpatients stay in previous six months (tertiles)	Continuous	Tertiles (0-24; 25-65; 66- 185 days)	Not included
Days of outpatient contact in	Continuous	Tertiles	Not included

previous six months (tertiles)		(1-2; 3-8; 9-117 days)	
Previous Community Treatment Order	Categorical (Yes/ no)	Not included	Not included
Number of Antipsychotic medication previously used	Continuous	Not included	Not included
Previous Clozapine use	Categorical (yes/ no)	Not included	Not included
Previous long-acting injectable antipsychotic use	Categorical (yes/ no)	Not included	Not included
Dose	Not included	Not included	Dose as a percentage BNF maximum dose- continuous Olanzapine equivalence dose- categorical 1-10mg; 11-20mg; 21+mg
Time known to SLAM	Not included	Not included	Continuous in days
Smoking	Not included	Not included	Categorical (yes/no)

Age

Age was derived from patient's date of birth, which is a structured field in PJS and was calculated at the time the patient entered the cohort (e.g. in Chapter 7, this was at patient's index discharge date). Information on date of birth was available for 99.7 per cent of the sample. In each project, a likelihood ratio test was used to determine whether it was appropriate to use age as either a continuous or a categorical variable in the analysis (for a likelihood ratio test definition please see page 116).

Gender

Gender was derived from a structured field in PJS and classified as either male or female. Gender information was available for all patients included in the projects.

Ethnicity

Ethnicity was derived from a structured field in PJS. There were seventeen ethnic groups in the source data field (African; any other Asian background; any other black background; ant other ethnic group; any other mixed background; any other white background; Bangladeshi; British; Caribbean; Chinese; Indian; Irish; none; not stated; Pakistani; white and Asian; white and black African), which were collapsed into smaller categories due to small cell sizes. Please refer to Table 4.2 for more information on how this variable was categorised in each project. Information on ethnicity was available for 98.65% of patients in the cohort.

Relationship status

Relationship status was derived from structured fields and has a total of eight categories, which were re-categorised as follows: "in a relationship" (cohabitating, married or civil partnership) and "not in a relationship" (single, divorced, separated, widowed, unknown). The completion of this field (i.e. excluding those unknown) was 93.48 per cent.

Employment status

Employment status was derived from a structured field and completed for 40.49 per cent of the sample (excluding those unknown). It contained sixteen categories, which were re-categorised as follows: "paid employment" (employed; other employment status; paid employment; part-time employment; self-employed) and "not in paid employment" (full-time student; full-time student school age; not known; not applicable; not disclosed; not known; other; registered disabled; retired; unemployed; volunteer).

Social deprivation

To estimate socioeconomic deprivation, the area-level index of multiple deprivation was used. It was derived by linking the patients' postcode to UK Census data for 2007. This was performed on Lower Super Output Areas (LSOA), which cover on average 1,500 residents per area unit (DCLG 2011). This index is based on seven domains of deprivation: employment, income, education, health, barriers to housing and services, crime, living environment, which are weighted and combined into an overall score of multiple deprivation (DCLG 2011). Homelessness was considered as an additional category in this

variable (Noble et al. 2008) for patients with no fixed abode. Patient postcode information was available for 98.50 per cent of the cohort.

Comorbid mental health diagnoses

Comorbid mental health diagnoses were derived from structured fields from the source data and supplemented by information derived from free text. Information was derived for depression (ICD-10 Code: F32, F33); substance use (ICD-10 Code: F10-16); and personality disorder (ICD-10 Code: F60; F61). Each comorbid diagnosis was coded as a binary variable, where '1' was allocated to patients who have received that particular diagnosis. All other patients were coded as '0'.

Health of the Nation Outcome Scale (HoNOS)

Clinical symptom presence/severity was estimated from the Health of the Nation Outcome Scale (HoNOS). HoNOS is a clinical outcome instrument in wide routine use, composed of 12 items designed to measure behaviour, impairment, symptoms, and social functioning (Wing et al. 1998). Items are scored on a scale of 0 (no problem) to 4 (severe to very severe problem). Due to small cell sizes, subscale scores were collapsed into three categories: 0 "not a problem"; 1 "minor problem requiring no action"; 2–4 ''significant problem'' (Hayes et al. 2012). The internal consistency of HoNOS has been estimated as moderately high (Cronbach's α=0.59-0.76) (Patterson et al. 2013); inter-rater reliability range 0.03 to 0.65 (mean 0.395) (Patterson et al. 2013; Delaffon et al. 2012); and test –retest reliability ranges between 0.33 and 0.80 (mean 0.57)(Patterson et al. 2013; Delaffon et al. 2012). At least one

HoNOS was completed for 84.46 per cent of the cohort; however its use was sometimes restricted by the timing of the completion of the scale. For example in Chapter 7, a HoNOS had to be completed after the index discharge date.

Inpatient admissions

The number of days spent as an inpatient was extracted from structured fields in PJS. In each project, a likelihood ratio test was used to determine whether to use this variable as a continuous or categorical in the analysis.

Outpatient contact

Previous outpatient contact was determined through the days each person had received face-to-face contact as recorded in structured fields in PJS. Multiple events on a single day were counted as one day of clinical contact, whilst clinical contact with outpatient services during an inpatient admission was not counted. In each project, a likelihood ratio test was used to determine whether to use this variable as a continuous or categorical in the analysis.

Time known to SLAM

This variable is described in Chapter 8 section 8.3.7. I identified the lengths of time, in days, each patient was known to SLAM services at the index date, by examining all structured and free-text records available since 1st January 2007 up until the point the patient qualified for the antipsychotic polypharmacy or monotherapy group. A likelihood ratio test was used to determine whether to use this variable as a continuous or categorical in the analysis.

Community treatment orders

I identified all patients who had received a community treatment order (CTO) prior to the start of follow-up [CTOs refer to a conditional discharge from inpatient admission, commonly implemented for a period of six months to improve adherence to medication and promote regular contact with services (DoH 2007)]. Information on CTOs was extracted from structured fields and coded as a binary variable, where 1 indicated the presence of a previous CTO.

Prior antipsychotic medication use

Information on antipsychotic medications was extracted from structured medication fields and supplemented by information in free–text fields, and SLAM pharmacy records, see section 4.4 above.

Antipsychotic dose

Information on antipsychotic dose value, unit and frequency was extracted from structured and free-text fields (using NLP), for both monotherapy and polypharmacy, where such information was available. Antipsychotic polypharmacy cases where dose was not available for all antipsychotics that were part of the polypharmacy were not included. I validated prescribed dose manually by examining 43 randomly selected patients from the cohort. Precision (Positive predictive value) was observed to be 0.81. For details on the validation process see section 4.7.1 above. Chapter 8 section 8.3.5 also provides further details on how dose was used in the study.

Smoking

The smoking NLP application described in section 4.4.3 was used to extract information on whether the patients have ever smoked. Patients were classified in two groups, those who have never smoked (coded as 0) and those who have in the past or are currently (at present/ at the time of the document) smoking (coded as 1).

4.9 Statistical analysis

STATA 13 was used to conduct all statistical analyses, apart from the studies described in Chapter 5 and 6, where STATA 12 was used. I built multivariable logistic regression models to investigate the associations between potential predictors and long-term antipsychotic polypharmacy (Chapter 6). Odds ratios (OR) and 95 per cent confidence intervals (CI) were reported for crude and fully adjusted associations. Multivariable Cox proportion hazard models were built to investigate: the risk for hospital readmission into secondary mental health care of patients discharged on antipsychotic polypharmacy (Chapter 7); and to examine the association between antipsychotic polypharmacy and the risk of all-cause mortality (Chapter 8). 'Cox proportion hazard model is a type of survival analysis where covariates are used to predict the hazard function. The model can accommodate multiple covariates that also act multiplicatively on the hazard function. The baseline hazard function is not specified however it must be positive. In this thesis, time for the Cox analysis began at the point a patient had been on a given antipsychotic regimen (the exposure) for six or more months. This approach assumes that the exposure carries forward and does not take into account that a patient may go off and back on different

treatment regimens. An alternative approach could have been time dependent exposure, which takes into account that a patient can have multiple antipsychotic episodes (e.g. antipsychotic monotherapy, polypharmacy and no antipsychotics) over a period of time. Unfortunately the data derived from CRIS did not have sufficient details (such as start and stop dates of medication) in order to be able to detect discrete pharmacological episodes. Therefore, I deemed Cox regression analysis as the most suitable approach.

Kaplan-Meier curves with a log-rank test were used to compare those prescribed antipsychotic monotherapy to polypharmacy in both analyses described in Chapter 7 and 8. In addition, prior to conducting the Cox proportional hazard models, the proportional hazard assumption was checked using a formal test of assumptions, which evaluates whether the hazard ratios estimated by the Cox change with time. This was done by splitting time into tertiles. A new variable (which was the interaction term between the time tertiles and the two medication categories) was then created. This variable was added to the Cox model, and using a likelihood ratio test, was compared against the unadjusted Cox model, to test if it offers a better fit. Furthermore, I used likelihood ratio tests to determine if it was appropriate to include covariates in the models as continuous variables comparing two Cox models, one with the continuous covariate and one where the continuous variable was spilt in categories (i.e. quartiles), where they were used as levels of a factor. If there was no significant difference between the two models, I used the variable as continuous. To examine the risk for cause-specific mortality and antipsychotic polypharmacy prescribing, I used competing risk regression

analysis (Chapter 8). In Chapter 7 and 8, I also used standard propensity score methods to reduce the effect of confounding by indication. Propensity scores were used in two ways: 1) a propensity score was built through a regression model which included all covariates in the specific project (refer to Chapter 7 section 7.3.4; and Chapter 8 section 8.3.8). I then included the propensity score in place of these covariates in the Cox model; 2) I constructed a fully adjusted Cox model, where I only included patients who were at risk of being prescribed monotherapy and polypharmacy based on their propensity score. This was decided by summarising the distribution of the propensity scores for both medication groups (antipsychotic monotherapy and polypharmacy) and selecting the area of overlap, as the propensity scores indicative of being at risk for both antipsychotic monotherapy or polypharmacy prescribing. Details regarding the specific 'at risk' scores have been added in the relevant sections in each respective project chapter (see page 194 and 235). Details for the specific projects analyses are available here: Chapter 6 section 6.3.4; Chapter 7 section 7.3.4; Chapter 8 section 8.3.8.

CHAPTER 5: DEVELOPING AND EVALUATING A NOVEL PROCESS OF EXTRACTING ANTIPSYCHOTIC POLYPHARMACY DATA FROM ELECTRONIC HEALTH RECORDS

The contents of this chapter have contributed to the following:

Publication in peer-reviewed journal (full text available in Appendix A)

Kadra, G., Stewart, R., Shetty, H., Jackson, R. G., Greenwood, M. A., Roberts, A., Chang, C.-K., MacCabe, J. H., and Hayes, R. D. (2015). Extracting antipsychotic polypharmacy data from electronic health records: developing and evaluating a novel process. *BMC Psychiatry*, *15*(1), 166. doi:10.1186/s12888-015-0557-z

5.1 Abstract

Background: Antipsychotic prescription information is commonly derived from structured fields in clinical health records. However, utilising diverse and comprehensive sources of information is especially important when investigating less frequent patterns of medication prescribing such as antipsychotic polypharmacy. This study describes and evaluates a novel method of extracting antipsychotic polypharmacy data from both structured and free-text fields in electronic health records (EHRs), and its use for research purposes.

Methods: Using anonymised EHRs, I identified a cohort of SMI patients who were treated in SLAM NHS Foundation Trust mental health care services between 1 January and 30 June 2012. Information about antipsychotic co-prescribing was extracted using a combination of natural language processing and a bespoke algorithm. The validity of the data derived through this process was assessed against a manually coded gold standard to establish precision and recall. Lastly, I estimated the prevalence and patterns of antipsychotic polypharmacy.

Results: Individual instances of antipsychotic prescribing were detected with high precision (0.94 to 0.97) and moderate recall (0.57-0.77). I detected baseline antipsychotic polypharmacy (2 or more antipsychotics prescribed in any 6-week window) with 0.92 precision and 0.74 recall and long-term antipsychotic polypharmacy (antipsychotic co-prescribing for 6 months) with 0.94 precision and 0.60 recall. Of the 7,201 SMI patients receiving active care during the observation period, 338 (4.7%; 95% CI 4.2-5.2) were identified as receiving long-term antipsychotic polypharmacy. Two second-generation

antipsychotics (64.8%); and first-second generation antipsychotic combinations were most commonly co-prescribed (32.5%).

Conclusions: These results suggest that this is a potentially practical tool for identifying polypharmacy from mental health EHRs on a large scale. Furthermore, extracted data can be used to allow researchers to characterize patterns of polypharmacy over time including different drug combinations, trends in polypharmacy prescribing, predictors of polypharmacy prescribing and the impact of polypharmacy on patient outcomes.

5.2 Background

5.2.1 Existing research using electronic health records (EHRs)

Clinical health records have been previously used to examine antipsychotic medication prescribing (Munk-Jørgensen et al. 2014; Amaddeo 2014); however, the potential value of EHRs remains underexplored. In the context of mental health care, EHRs contain large volumes of detailed information in free text and structured fields, providing an important resource for conducting analyses using large samples and investigating a multitude of patient characteristics and outcomes simultaneously (Stewart 2014).

Studies investigating prescription databases (Ganguly et al. 2004; Taylor et al. 2003; Leckman-Westin et al. 2014) have been successful in deriving medication data for large populations and over long periods of time by predominately extracting data from structured fields (such as drop down menus, or dedicated response boxes) (Leckman-Westin et al. 2014). However, such studies have been restricted by the limited nature of the derived information (Taylor et al. 2000). Data on drug prescription, as well as related contextual information, is frequently embedded in free-text fields in mental health EHRs and this may be the only source of such information in the absence of e-prescribing or a Primary Care Linkage. Traditionally, extracting free-text information has necessitated manual coding (where a researcher reads free text and codes it by hand according to a defined set of coding rules) (Su et al. 2014), which is time and labour intensive and therefore not always feasible on a large scale. This can result in investigating a smaller

than ideal sample (Centorrino et al. 2008; Brown et al. 2000; Suzuki et al. 2008; Centorrino et al. 2004). EHR text has been analysed automatically using techniques such as NLP for a variety of purposes (Meystre et al. 2008). However, although this has involved the identification of drugs (Uzuner et al. 2010), as far as I am aware, there have been no attempts to develop and validate techniques for characterising meta-data such as polypharmacy.

5.2.2 Antipsychotic polypharmacy

Automated extraction of information on medication prescribing is potentially valuable for investigating specific but important clinical prescribing patterns such as the practice of prescribing more than one antipsychotic drug simultaneously, known as antipsychotic polypharmacy, which may be challenging to identify through manual searches. The prevalence of antipsychotic polypharmacy in routine clinical practice has been estimated to vary between 10-30% (Gallego et al. 2012) in people with serious mental illness (SMI), despite little empirical evidence to support benefits associated with its use (Lochmann van Bennekom et al. 2013), and associations with adverse health outcomes, such as increased physical health problems (e.g. weight gain, diabetes, metabolic syndrome, dyslipidaemia) and death (Chang et al. 2010; Reynolds & Kirk 2010; Brown 1997). Therefore, we need to gain a better understanding of the clinical characteristics that predict antipsychotic polypharmacy prescribing and determine associated health outcomes. One way to achieve this is through research using “real-life” data available in EHRs. Antipsychotic polypharmacy is thus an important exposure and

potential confounder to be considered in studies investigating the impact of antipsychotic drugs in clinical settings and yet, as stated, is difficult to characterise on a large scale.

5.2.3 Aims

The aim of this chapter is to present and evaluate a novel process of extracting antipsychotic polypharmacy data from a large EHR data resource, utilising information available from both structured and free-text fields. In addition, I used the processed data to estimate the prevalence of antipsychotic polypharmacy, as well as patterns in co-prescribing, for a six-month period in 2012.

5.3 Methods

5.3.1 Settings

This investigation used electronic mental health records from SLAM secondary health care (see Chapter 4 section 4.2, for a detailed description of SLAM electronic health records and CRIS).

5.3.2 Sample

All adult service users with SMI diagnosis of schizophrenia (ICD-10: F20), schizoaffective disorder (F25) or bipolar disorder (F31) who received care from SLAM between January and June 2012 were considered.

5.3.3 Deriving antipsychotic polypharmacy data from EHRs

All antipsychotic drugs listed in the BNF 65 (British National Formulary 2015) were considered. The BNF is a reference book containing information on pharmacology and prescribing of many medicines (including 29 antipsychotics) available on the British National Health Service (NHS). Structured fields for recording medications data are present in the source EHR interrogated by CRIS, and were used in this analysis, but these are infrequently completed. Information was also extracted from SLAM pharmacy records, although this only covers particular drugs that are subject to monitoring by the pharmacy, such as clozapine. Most antipsychotic prescription information was extracted from free-text fields, including those

recording clinician-patient encounters, and correspondence between health care professionals.

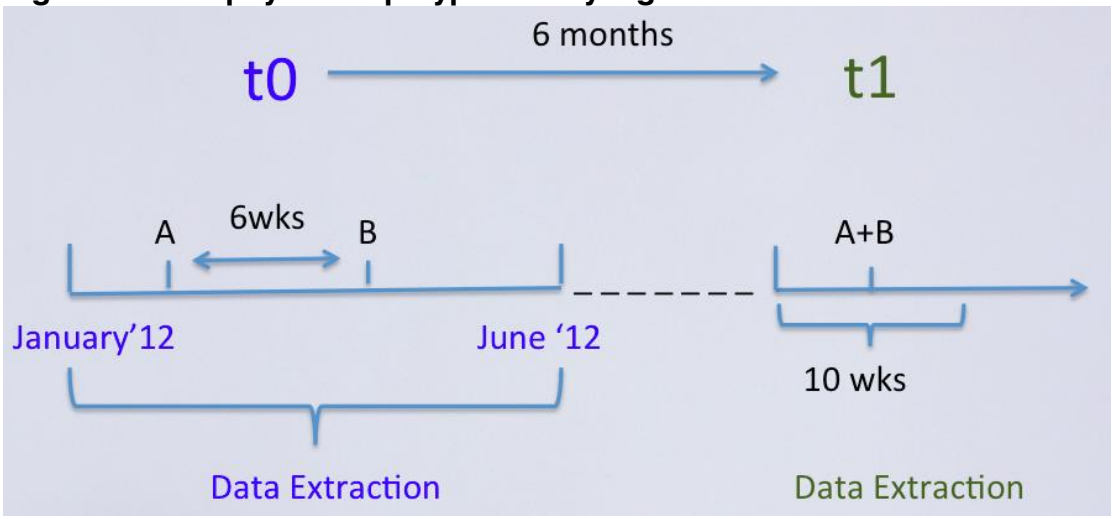
I extracted antipsychotic medication data from the free text with a NLP information extraction application developed using GATE software (Cunningham et al. 2013; Cunningham 2002), a suite of tools that facilitates the use and development of NLP applications and features. NLP is able to identify and exclude negation statements and speculations about future prescribing and instances in the text where the drug is mentioned as being taken by a person other than the patient. In addition to this, the application allows the user to extract grammatical features, which I used to create specific filters to maximize precision and recall of antipsychotic prescribing. Two filters were initially applied: all instances of medication prescription that were not prescribed at the 'present time' (this refers to medication prescribed up until today, or from today with regard to the date the document was written) and that did not include a dose value were excluded at the point of data extraction. Therefore, any mentions of the drug without such supporting prescription information were not extracted, as these were deemed too imprecise.

5.3.4 Antipsychotic polypharmacy algorithm

Antipsychotic polypharmacy was ascertained using an algorithm comprising two steps, as illustrated by Figure 5.1. In step one, case records were examined to determine whether two or more antipsychotics were prescribed within a six-week period between January and June 2012. Co-prescribing at

this stage (t0) was defined as baseline polypharmacy. In other words, t0 was the date on which an additional antipsychotic was detected in the clinical records that was prescribed within 6 weeks of the first antipsychotic. At stage two, data on all patients with antipsychotic polypharmacy at baseline were re-examined six months after t0. A manual inspection of the data revealed that I was initially omitting outpatients who had less frequent clinical appointments and longer periods of time with no entry in the clinical record. Consequently, I specified that the follow-up search should begin at the point of first clinical event occurring six months or more after t0, which I designated as t1. Antipsychotic information was extracted from the clinical records, for the first ten weeks following t1, to determine whether the same set of antipsychotics were prescribed; if so, this was classified as ‘long-term’ polypharmacy. In order to qualify for polypharmacy at t1, at least two of the antipsychotics from t0 had to be present at t1.

Figure 5.1 Antipsychotic polypharmacy algorithm.



During further development of the algorithm, I established that NLP-derived time and dose features were not sufficient to identify cases of antipsychotic polypharmacy, as they were not able to completely exclude historic medication information in clinical summaries, resulting in false positive instances (this refers to cases that are not true polypharmacy, but are detected as such by the application). Therefore, two additional filters were devised, applying the following exclusions: i) antipsychotic drugs with only a single annotation (by *annotation* I mean the identification and marking of spans of text that represent the prescribing of an antipsychotic) for the entire study period; and ii) antipsychotic drugs with multiple annotations but where all annotations were restricted to a single document for the entire study period. I reasoned that it was unlikely that a patient prescribed particular medication would have it mentioned in their notes only once over this period or only on a single day (e.g. a single document) over this period.

To evaluate the performance of the data extraction process (NLP application and antipsychotic polypharmacy algorithm), I measured two indicators of validity: precision and recall. Precision (equivalent to positive predictive value in psychometrics) represents the proportion of patients identified as polypharmacy considered to be 'true positive', out of all cases identified as such by the algorithm. Recall (equivalent to sensitivity) represents the proportion of patients on given medications who were identified as such by the algorithm.

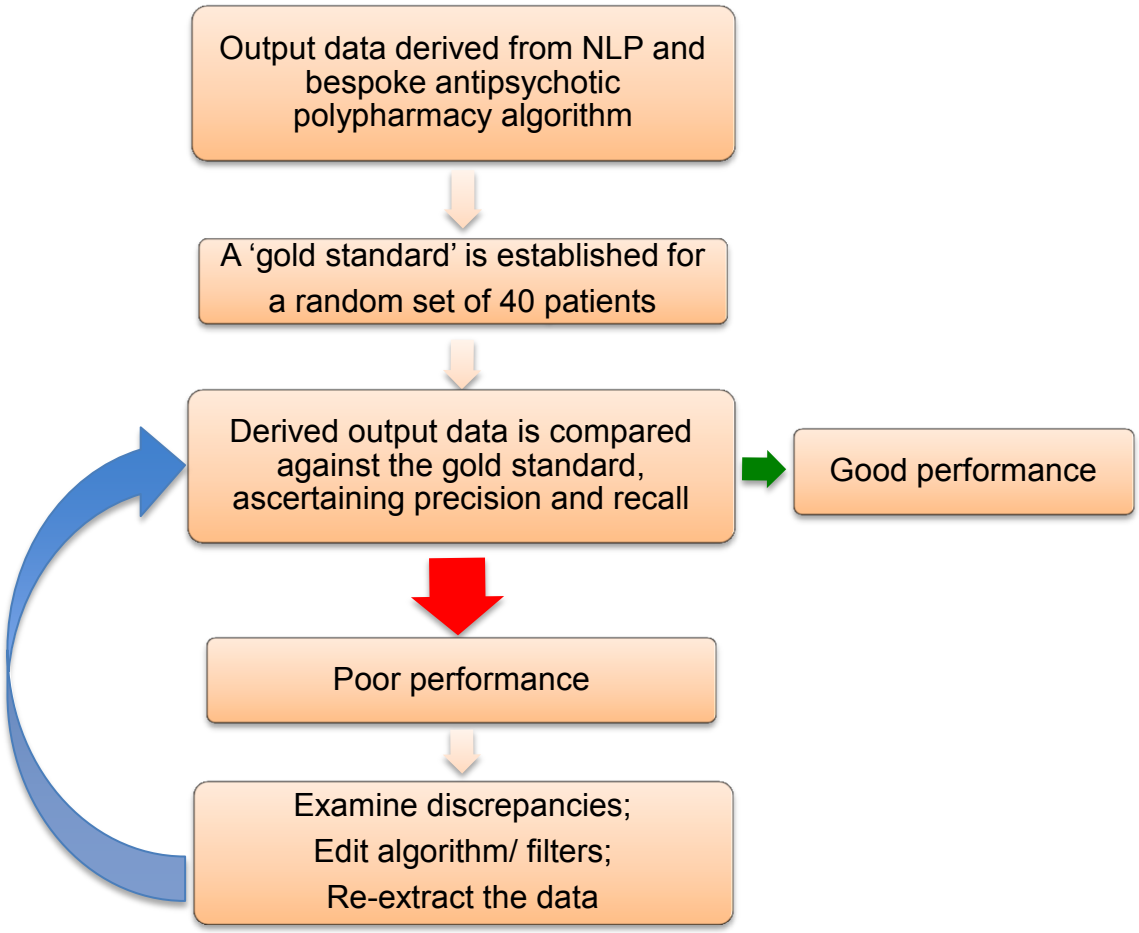
5.3.5 Validation

Prior to testing the performance of the antipsychotic polypharmacy algorithm, I examined the NLP application of extracting information for specific antipsychotic agents prescribed at individual points in time (i.e. instances rather than episodes). I examined and manually coded free-text records over a 6-month period (January to June 2012) for a subset of 120 randomly selected patients, who had a mention of two or more antipsychotics at any point between January and June 2012. I chose to examine six frequently prescribed antipsychotics (Leucht et al. 2013) under the assumption that these medications would have a larger number of annotations for examination. Precision and recall for the extraction of clozapine prescriptions using this NLP algorithm is not included here as this has been described previously (Hayes et al. 2014). The instances of antipsychotic prescribing varied from 328 to 1150 instances, per antipsychotic agent. I ran the NLP application over this set of unseen documents (that had not been used in the development of the NLP application) and compared the results to the manual coding of the same dataset.

As illustrated by Figure 5.2, the final antipsychotic polypharmacy algorithm was derived following an iterative validation process. From those that were initially identified as being on polypharmacy by the application, I selected a random subset of 40 patients and manually coded their clinical records for antipsychotic polypharmacy, in order to ascertain its 'true' occurrence (also referred to as the 'gold standard'). The gold standard for antipsychotic polypharmacy at t0 included instances where: both antipsychotics are

mentioned as present; evidence of one antipsychotic added to an existing antipsychotic; two different antipsychotics are mentioned in the clinical notes within six weeks of each other. At this stage I did not attempt to distinguish between long-term and short form of polypharmacy such as PRN or cross-titration. Short forms of antipsychotic polypharmacy were filtered out at t1, as these cases were unlikely to have continued for six or more months. The gold standard for antipsychotic polypharmacy at t1 included instances where: there is evidence that two or more antipsychotics are prescribed at least six months from the mention at t0. The extracted data were then compared against the gold standard to ascertain the validity of antipsychotic polypharmacy and to examine discrepancies. Instructions within the algorithm were then added or edited accordingly until a satisfactory performance was obtained. Good and poor performance was decided informally. Performance of 0.80 or above was considered as a good. To confirm generalizability, the 'final' algorithm was tested on a new subset of 30 randomly selected patients. To estimate recall, from all patients active in the observation period, I selected a random subset of 110 individuals.

Figure 5.2 Antipsychotic polypharmacy validation process.



5.3.6 Analysis

Having assessed the precision and recall of the NLP application and antipsychotic polypharmacy algorithm, using the antipsychotic polypharmacy algorithm I estimated the prevalence of baseline and long-term (≥ 6 months) antipsychotic polypharmacy. Prevalence estimates and 95% confidence intervals were reported for baseline and long-term polypharmacy, as well as for long-term polypharmacy distribution by antipsychotic class and by individual agent.

5.4 Results

5.4.1 Validation

As summarised in Table 5.1, the NLP application was able to identify individual instances of the selected antipsychotic agents with high precision, although recall levels were more modest. For the antipsychotic polypharmacy algorithm, the precision obtained from the final validation set of 30 patients was 0.92 for baseline and 0.94 for long-term antipsychotic polypharmacy. Recall was measured at 0.74 and 0.60 for baseline and long- term antipsychotic polypharmacy respectively.

Table 5.1 Precision and recall per individual antipsychotic agent.

Antipsychotic agent	N*	Precision (%)	Recall (%)
Amisulpride	619	97.4	61.0
Flupentixol	328	94.1	77.0
Haloperidol	747	94.0	57.0
Olanzapine	1150	95.0	69.3
Risperidone	737	95.0	64.1
Zuclopenthixol	390	97.0	67.5

***** Number of annotations per antipsychotic

5.4.2 Main results

I determined that 7,201 adult patients with SMI diagnosis were active in SLAM services between January and June 2012. In total 830 (11.5%;95% CI: 10.8-12.3) patients were prescribed two or more antipsychotics in any six weeks between January and June 2012, and 338 (4.7%; 95% CI: 4.2-5.2) were prescribed the same set of antipsychotics for six or more months. Twenty patients prescribed antipsychotic polypharmacy at t0 died before t1. I was unable to determine reasons other than the above for not continuing antipsychotic polypharmacy between t0 and t1.

Amongst patients prescribed long-term antipsychotic polypharmacy, co-prescribing two or more SGAs was most common (n=219; 64.8%; 95% CI: 59.7- 69.9), followed by FGA and SGA (n=110; 32.5%; 95% CI: 27.5- 37.6) combinations, and two or more FGAs (n=9; 2.7%; 95% CI: 0.9- 4.4).

Table 5.2 summarises long-term co-administration patterns by individual agents. Similarly to co-administration by class, the combination of two (or more) FGAs was relatively rare. The most common antipsychotic used in combination was clozapine, combined with at least one other SGA.

Table 5.2 Prevalence of long-term antipsychotic polypharmacy combinations (n=338).

Antipsychotic medication	n	Plus at least one other FGA* n (%)	Plus at least one other SGA* n (%)
First Generation Antipsychotics (FGA)*			
Chlorpromazine	8	1 (12.5)	7 (87.5)
Flupentixol	26	6 (23.1)	20 (76.9)
Fluphenazine	4	2 (50.0)	2 (50.0)
Haloperidol	30	5 (16.7)	25 (83.3)
Levomepromazine	1	-	1 (100.0)
Pericyazine	1	1 (100.0)	-
Pimozide	2	-	2 (100.0)
Pipothiazine	10	2 (20.0)	8 (80.0)
Sulpiride	33	1 (3.0)	32 (97.0)
Trifluoperazine	3	-	3 (100.0)
Zuclopenthixol	25	-	25 (100.0)
Second Generation Antipsychotics (SGA)*			
Amisulpride	118	18 (15.3)	100 (84.7)
Aripiprazole	79	12 (15.2)	67 (84.8)
Clozapine	168	27 (16.1)	141 (83.9)
Olanzapine	95	44 (46.3)	51 (53.7)
Paliperidone	40	8 (20.0)	32 (80.0)
Quetiapine	21	11 (52.4)	10 (47.6)
Risperidone	64	21 (32.8)	43 (67.2)

* These are overlapping categories; antipsychotic combinations may include additional FGAs or SGA where patients are prescribed more than 2 antipsychotics simultaneously.

5.5 Discussion

To my knowledge, this is the first report investigating the feasibility and yield for a process of extracting antipsychotic polypharmacy data from both structured and free-text fields in EHRs, using a combination of NLP and a bespoke algorithm. This process enabled me to identify instances where specific antipsychotic agents were prescribed, then classify baseline and long-term antipsychotic polypharmacy profiles over time.

The NLP application combined with the antipsychotic polypharmacy algorithm performed at a high precision, suggesting that individuals classified as being prescribed antipsychotic polypharmacy were very likely to be classified correctly. The moderate recall suggested that I was less able to detect all antipsychotic polypharmacy cases. In designing the antipsychotic polypharmacy algorithm, I noticed that some of the rules used to decrease the false positive cases of antipsychotic polypharmacy filtered out some of the 'true' cases, requiring a trade-off decision. Although detecting all cases is desirable, especially when investigating relatively uncommon phenomenon such as polypharmacy, I chose to prioritise precision over recall due to the large number of non-cases in the sample, which might be expected to dilute the impact of any such misclassification in future analyses. Similarly, the NLP application was developed to favour precision over recall. In this study I considered date-specific recall when evaluating the NLP application for extracting individual medications; however, in longitudinal studies a single patient often has a number of documents containing the same prescription

information, therefore relatively low recall could be compensated for by combining results extracted from several documents.

I estimated that just under five per cent of all adult patients with SMI were prescribed two or more antipsychotics for six or more months. Although this is comparable to some research investigating antipsychotic polypharmacy with longer duration (Morrato et al. 2007) found 6.4% antipsychotic polypharmacy prevalence in a Medicaid population), it is somewhat lower in comparison to other previous research (10-30%) (Gallego et al. 2012). The lower prevalence could be attributable to a more conservative approach that was adopted in detecting antipsychotic polypharmacy, by examining long-term co-prescription with a minimum duration of six months. Some previous studies that have examined concomitant prescribing for 28 days (Jaffe & Levine 2003), 6 weeks (Broekema et al. 2007; Taylor et al. 2002) and 60 days (Ganguly et al. 2004; Suokas et al. 2012) may have included instances of 'as required' medication and switching. It is also possible that some polypharmacy cases were omitted because I prioritized precision over recall in developing the NLP application and algorithm. It is further possible that the low prevalence of antipsychotic polypharmacy that I have detected reflects a recent drive within UK health services to decrease antipsychotic polypharmacy prescribing. For example, Mace and Taylor (Mace & Taylor 2015) demonstrated that antipsychotic polypharmacy in inpatient settings can be reduced through regular patient reviews and collaborative work between clinicians and pharmacists. Their quality improvement programme managed to successfully reduce the rate of polypharmacy from 57% to 16% in inpatient settings and intensive care units.

This was clearly a substantial decrease and suggests that even though some patients may be more likely to be prescribed polypharmacy, this is not necessarily a long-term treatment management strategy and can be successfully transitioned to monotherapy.

On the other hand, the findings are consistent with previous research on antipsychotic co-administration, where two or more SGAs, and FGA-SGA combinations are found to be the most prevalent combinations in clinical settings (Gallego et al. 2012; Broekema et al. 2007; Taylor et al. 2002; Centorrino et al. 2005; Ganguly et al. 2005).

Previous research has suggested that olanzapine and risperidone are most commonly combined in co-prescribing (Broekema et al. 2007; Bernardo et al. 2012). Clozapine was the most commonly co-prescribed antipsychotic in our sample. Although the therapeutic benefits of clozapine co-prescribing has been previously called into question (Taylor et al. 2011), this antipsychotic remains one of few that has some empirical support when used in polypharmacy (Freudenreich & Goff 2002). Furthermore, most research to date has examined shorter periods of antipsychotic polypharmacy (i.e. 6 weeks)(Broekema et al. 2007), whereas studies investigating long-term antipsychotic polypharmacy have reported a higher prevalence of clozapine as a component (Ganguly et al. 2004). Clinically, this may indicate that patients persistently prescribed antipsychotic polypharmacy over longer periods of time are different from those on other forms of antipsychotic polypharmacy (e.g. short bouts of co-prescribing); more specifically, it is likely

that this sub-group are more unwell and possibly treatment-refractory (Lerner et al. 2004).

5.5.1 Strengths

The process of extracting medication data from EHRs has a number of advantages. For example, in instances where structured fields are poorly populated or incomplete, using supplementary information available in free-text fields provides more detailed and complete information of treatments. A particular advantage of NLP is its ability to take into account the linguistic context around terminology of interest. Therefore, I was able to identify and exclude negation statements, past rather than current prescribing, speculations about future prescribing and instances in the text where the drug is mentioned as being taken by a person other than the patient. Furthermore, the antipsychotic polypharmacy algorithm allowed me to distinguish between different modes of polypharmacy administration, such as shorter (which would potentially include 'as required' and switching occurrences) and longer forms of co-prescribing.

Data from EHRs are a source of rich and diverse contextual information, much of which may be embedded in free-text fields. The process described here may be adapted to extract an array of factors, which may predict antipsychotic polypharmacy and/or confound associations between antipsychotic polypharmacy and mental or physical health outcomes. Routinely collected EHRs capture a range of populations, such as patients in

different clinical settings (e.g. inpatients/ outpatients) and with different socio-demographic profiles who have been previously under-represented and/or under-investigated in research. Moreover, EHRs more closely approximate real-life clinical practice than formal research projects involving *de novo* data collection, permitting the identification of trends in medication prescribing that are not otherwise captured by clinical trials. This could be valuable information that can be fed back into prescribing guidelines. Finally, the historic nature of EHRs allows longitudinal research, where medication profiles can be examined in relation to multiple predictors and outcomes.

5.5.2 Limitations

The protocol for extracted antipsychotic polypharmacy data has a number of limitations, which should be borne in mind. As indicated by the recall for individual antipsychotics and long-term antipsychotic polypharmacy, the approach may under-estimate the true prevalence of antipsychotic polypharmacy. Furthermore, the output data depends on the quality and accuracy of clinical entries (Stewart et al. 2009), which may vary by clinicians and services. Finally, it is important to note that I examined antipsychotic polypharmacy over a relatively short period of time, and it is possible that the data reflects a specific pattern in medication prescribing during that period.

5.5.3 Conclusions

In conclusion, I was able to develop a novel process for extracting antipsychotic polypharmacy information from a secondary care EHR at high

levels of precision. The implications for effectively utilising clinical information for research purposes are manifold. De-identified clinical records are reflective of health care service provision for large and diverse populations, therefore enabling researchers to examine clinical characteristics that predict antipsychotic profiles and confound the relationship with negative health outcomes. Furthermore, EHRs allow researchers to prospectively examine multiple outcomes in relation to polypharmacy such as mortality and physical health consequences; therefore, advancing our understanding of the impact of antipsychotic profiles on patients.

CHAPTER 6: PREDICTORS OF LONG-TERM ANTIPSYCHOTIC POLYPHARMACY PRESCRIBING IN SECONDARY MENTAL HEALTH CARE

The contents of this chapter have contributed to the following:

Publication in peer-reviewed journal (full text available in Appendix B)

Kadra, G., Stewart, R., Shetty, H., Downs, J., MacCabe, J. H., Taylor, D., & Hayes, R. D. (2016). Predictors of long-term (≥6 months) antipsychotic polypharmacy prescribing in secondary mental health care. Schizophrenia Research, 174, 1-3.

6.1 Abstract

Background: The predictors of long-term antipsychotic polypharmacy initiation are poorly understood. Existing research has been hampered by residual confounding, failure to exclude cross-titration, and difficulties in separating the timing of predictors and antipsychotic polypharmacy administration.

Methods: Using data from the SLAM case register, I identified all adult patients with SMI who were receiving care between 1st July 2011 and 30th June 2012. Exposures measured between 1st July and 31st December 2011 included socio-demographic, socioeconomic, clinical and service use characteristics. I then determined if long-term antipsychotic polypharmacy (six or more months) had been initiated between 1st January and 30th June 2012. Multivariable logistic regression models, adjusted for socio-demographic and socioeconomic factors, were built to investigate the associations between the above factors and the initiation of long-term antipsychotic polypharmacy.

Results: I identified 6857 adults with SMI receiving SLAM care, of whom 115 (1.7%) were newly prescribed long-term antipsychotic polypharmacy. In the adjusted models, predictors of long-term antipsychotic polypharmacy initiation included: symptoms (severity of hallucinations and/or delusions), previous treatments (clozapine and long-acting injectable antipsychotic agents), service use (more contact with outpatient services, community treatment order receipt), social factors (higher area-level deprivation, homelessness) and socio-demographic status (younger age, not in a relationship).

Conclusion: The findings highlight that certain patient groups are at an increased risk for long-term antipsychotic polypharmacy initiation. Identifying

these groups earlier in their treatment could encourage clinicians to employ a broader range of interventions in addition to pharmacotherapy to reduce the risk of antipsychotic polypharmacy prescribing.

6.2 Background

Antipsychotic polypharmacy (the concomitant administration of two or more antipsychotics) remains common practice in treatment of serious mental illnesses. Its prevalence is estimated to vary between 10-30% (Freudenreich & Goff 2002; Gallego et al. 2012), despite current guidelines recommending against antipsychotic polypharmacy use, except during clozapine augmentation (APA 2010; Lochmann van Bennekom et al. 2013; NICE & NCCMH 2013), and evidence of associations with increased mortality (Ganguly et al. 2004; Joukama et al. 2006; Waddington et al. 1998) and physical health problems (including metabolic and cardiovascular disorders) (Ganguly et al. 2004; Raedler 2010). Examining factors that may predict antipsychotic polypharmacy prescribing is key to understanding its continued use.

To date, male gender (Ganguly et al. 2004; Morrato et al. 2007; Suokas et al. 2012; Santone et al. 2011), and younger age (Kreyenbuhl et al. 2007; Morrato et al. 2007; Suokas et al. 2012) have been found to be associated with antipsychotic polypharmacy, but there has been a lack of information on socioeconomic factors such as social deprivation. Antipsychotic polypharmacy has been found to be associated with more frequent previous hospital admissions (Ganguly et al. 2004; Kreyenbuhl et al. 2007; Ortiz et al. 2016), longer duration of previous admissions (Suokas et al. 2012), higher number of previous outpatient contacts (Ganguly et al. 2004; Kreyenbuhl et al. 2007) and previous antipsychotic medication use (Barbui et al. 2006; Suokas et al. 2012). Findings regarding the role of clinical symptoms in antipsychotic

polypharmacy prescribing have been inconsistent (Barbui et al. 2006; Biancosino et al. 2005; Gallego et al. 2012; Moilanen et al. 2016).

Previous research has examined antipsychotic polypharmacy of varying duration (Broekema et al. 2007; Clark et al. 2002; Faries et al. 2005; Ganguly et al. 2004; Ito et al. 2005; Jaffe & Levine 2003; Janssen et al. 2005) and has often included polypharmacy during cross-titration, which has hampered definitive conclusions on predictors. More recently research has begun to investigate antipsychotic polypharmacy with longer duration (>60 days) in an attempt to distinguish between cross-titration and long-term treatment (Barbui et al. 2006; Ganguly et al. 2004; Kreyenbuhl et al. 2007; Morrato et al. 2007). However, cross-titration is a process that can take up to 10 weeks to complete (Correll et al. 2011; Lochmann van Bennekom et al. 2013); therefore studies examining antipsychotic polypharmacy with a duration of 70 days or less cannot definitively exclude switching. Aside from heterogeneity in antipsychotic polypharmacy definition, investigations to date have risked residual confounding due to limited covariates in models (Centorrino et al. 2004; Faries et al. 2005). Furthermore, limitations in being able to distinguish temporally between the occurrence of antipsychotic polypharmacy prescribing and associated factors make it difficult to determine if the latter are predictors or consequences (Kreyenbuhl et al. 2007). Other limitations include small homogeneous inpatient samples (Centorrino et al. 2004; Centorrino et al. 2005), restricting generalizability.

Using data derived from a large de-identified electronic health records case register with near-universal coverage of a defined population, I investigated socio-demographic, socioeconomic, clinical, and service-use predictors of long-term antipsychotic polypharmacy initiation in SMI.

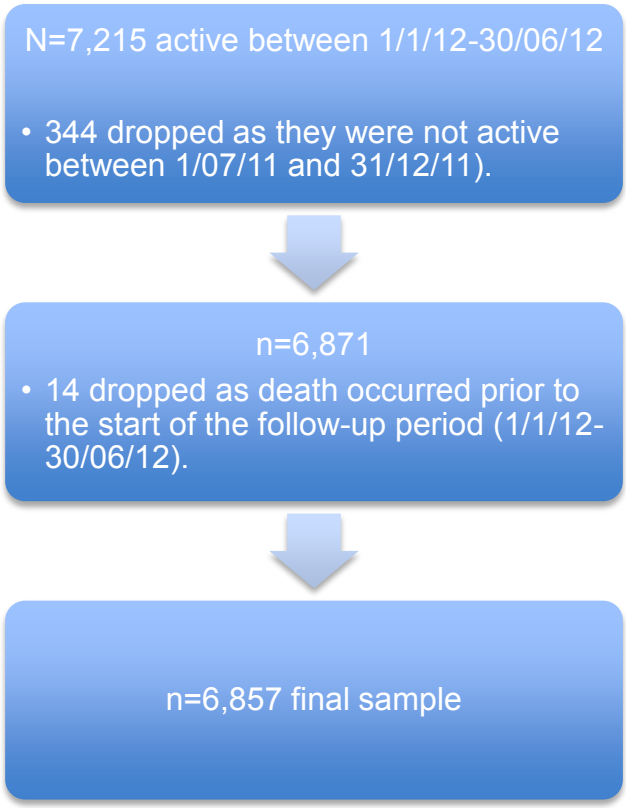
6.3 Methods

6.3.1 Study design, data source and study sample

This was a retrospective cohort study within a comprehensive register of patients treated with SMI in the SLAM NHS Foundation Trust (see Chapter 4 section 4.2 for a detailed description of SLAM electronic health records and CRIS).

Using CRIS, I ascertained all adult patients with a diagnosis of schizophrenia (ICD-10 code: F20.x), schizoaffective disorder (F25.x) or bipolar disorder (F31.x) and who were in contact with SLAM clinical services between 1st July 2011 and 30th June 2012 (Figure 6.1). All potential predictors were measured between 1st July and 31st December 2011. Antipsychotic polypharmacy initiation was determined for the period between 1st January and 30th June 2012, also referred to as the follow-up period. In other words, I began to search clinical records for antipsychotic polypharmacy on 1st January 2012.

Figure 6.1 Predictors of long-term antipsychotic polypharmacy: sample selection.



6.3.2 Outcome measures

The primary outcome was long-term antipsychotic polypharmacy initiation, defined as the concomitant prescription of two or more antipsychotic agents for at least six months, with the aim of minimising the likelihood of cross-titration being classified as polypharmacy. All service users who commenced antipsychotic polypharmacy at some point from 1st January to 30th June 2012, but who had not received antipsychotic polypharmacy in the 6 months prior to this were considered to have been 'initiated' on long-term antipsychotic polypharmacy. A detailed account of the method used for antipsychotic polypharmacy ascertaining in CRIS and the validation of this technique have been described in Chapter 5 section 5.3.4.

6.3.3 Explanatory variables

For a detailed description of these variables please refer to Chapter 4 section 4.8. Age was calculated on the 1st January 2012 and categorised by quartiles. The remaining socio-demographic and socioeconomic factors were derived from the last entry recorded prior to 1st January 2012. Seventeen ethnic group categories were collapsed into "White", "Black Caribbean", "Black African" and "Other", due to small numbers in some cells. Relationship status was defined as "in a current relationship" (cohabitating, married or civil partnership) and "not in a relationship" (single, divorced, separated, widowed, unknown). Employment status was recorded as being in "paid employment" (part-time, full-time, self-employed) and "not in paid employment" (unemployed, registered disabled, retired, student, looking after children, volunteer, in

training, not known, other). I used an area-level index of multiple deprivation to estimate socioeconomic status and categorised in tertiles based on the four catchment boroughs.

Clinical symptom presence/severity was estimated from the most recent HoNOS completed prior to 1st January 2012. HoNOS is a clinical outcome instrument in wide routine use, composed of 12 items designed to measure behaviour, impairment, symptoms, and social functioning (Wing et al. 1998). Items are scored on a scale of 0 (no problem) to 4 (severe to very severe problem). Due to small cell sizes, subscale scores were collapsed into three categories: 0 “not a problem”; 1 “minor problem requiring no action”; 2–4 ‘‘significant problem’’. Items that provided overlapping information to other variables used in this analyses were removed; therefore I did not include item 9 (assessing relationship problems), item 11 (assessing living conditions) and item 12 (assessing occupational problems). Item 8 (assessing other mental health problems) was also excluded, as the following comorbid diagnoses were ascertained using information available from free text and structured fields: i) depression [having received a diagnosis of depression (ICD-10: F32, F33) and/or scoring ‘mild’ to ‘significant’ on HoNOS item 7 problems with depressed mood]; ii) substance use [having received a diagnosis of substance use disorder (ICD-10: F10-16) and/or scoring ‘mild’ to ‘significant’ on HoNOS item 3 problems with drinking or drug-taking]; and iii) personality disorder [having received a diagnosis of personality disorder (ICD-10: F60; F61)].

I considered six measures of service use: i) previous outpatient contact was determined through the proportion of days each person had received face-to-face contact as an outpatient between 1st July and 31st December 2011 (multiple events on a single day were counted as one day of clinical contact, whilst clinical contact with outpatient services during an inpatient admission was not counted); ii) the number of days spent as an in-patient between 1st July and 31st December 2011 were determined separately; iii) I identified the number of previous antipsychotics used in the six months prior to follow-up; iv) I identified all patients who had received a community treatment order (CTO) [CTOs refer to a conditional discharge from involuntary inpatient admission, commonly implemented for a period of six months to improve adherence to medication and promote regular contact with services (DoH 2007)] prior to the start of follow-up (since 2007); dichotomous variables were generated to indicate whether, since 2007, patients v) had ever used clozapine or vi) ever used a long-acting injectable (LAI) antipsychotic agent.

6.3.4 Statistical Analysis

STATA 12 was used to conduct all statistical analyses. I estimated antipsychotic polypharmacy prevalence and incidence of newly initiated long-term antipsychotic polypharmacy in a six-month window. Further analyses focussed on predictors of long-term polypharmacy initiation. Multivariable models included potential confounders such as age, gender, ethnicity, relationship status, employment, and deprivation status. Clinical and service

use factors were not included as covariates due to possible over-adjustment for potential causal pathway factors.

Several sensitivity analyses were carried out. Firstly, I tested whether the timing of the HoNOS assessment had an effect on the association between clinical items and antipsychotic polypharmacy initiation, by restricting the analyses to HoNOS scores obtained within the last year prior to the start of follow-up. I further tested whether being a local resident (as opposed to patients referred from the wider national catchment area) had an effect on the association between antipsychotic polypharmacy and all exposure variables. Patients residing outside the local catchment area can be referred to SLAM services for specialist treatment, due to particularly severe or treatment-resistant symptoms. Therefore, this group could be inherently different to local patients.

6.4 Results

I identified 7201 adults with a SMI diagnosis who were receiving SLAM care between January and June 2012. I excluded 344 patients as they were not receiving care in SLAM services in the six months prior to 1st January 2012, resulting in a total sample size of 6857 patients. I found that 331 (4.8%) patients were receiving antipsychotic polypharmacy for six or more months between 1st January and 30th June 2012 (this sample is also referred to as overall antipsychotic polypharmacy) and 115 (1.7%) were newly initiated on long-term antipsychotic polypharmacy. Table 6.1 summarises the characteristics for the total cohort and by overall and newly prescribed antipsychotic polypharmacy.

Table 6.1 Cohort characteristics.

Variables	Total cohort N (%)	Antipsychotic polypharmacy* N (%)	Antipsychotic polypharmacy initiation* N (%)
Total sample	6857	331 (4.8)	115 (1.7)
Socio-demographic and socioeconomic factors			
Age			
16-35	1,737 (25.3)	117(35.3)	45 (39.1)
36-45	1,789 (26.1)	105 (31.7)	31 (27.0)
46-55	1,678 (24.5)	77 (23.3)	22 (19.1)
56+	1,653 (24.1)	32 (9.7)	17 (14.8)
Gender			
Female	2,821 (41.1)	111 (33.5)	40 (34.8)
Male	4,036 (58.9)	220 (66.5)	75 (65.2)
Ethnicity group			
White	3,124 (45.6)	125 (37.8)	41 (35.7)
Black Caribbean	992 (14.5)	54 (16.3)	16 (13.9)
Black African	1,851 (26.9)	106 (32.0)	43 (37.4)
Other	890 (13.0)	46 (13.9)	15 (13.0)
Relationship status			
Not in a relationship	6,052 (88.3)	311 (94.0)	111 (96.5)
In relationship	805 (11.7)	20 (6.0)	4 (3.5)
Employment status			
Not in paid employment	6,521 (95.1)	326 (98.5)	113 (98.3)
In paid employment	336 (4.9)	5 (1.5)	2 (1.7)
Deprivation level in area of residence			
Low level	2,087 (32.7)	95 (30.2)	25 (22.5)
Medium level	2,111 (33.1)	113 (35.9)	40 (36.1)
High level	2,107 (33.0)	97 (30.8)	42 (37.8)
Homelessness	74 (1.2)	10 (3.1)	4 (3.6)
Clinical factors			
Comorbid diagnosis			
Depression	3,437 (50.1)	165 (49.9)	50 (43.5)
Personality disorder	895 (13.1)	63 (19.0)	20 (17.4)
Substance use	1,956 (28.5)	103 (31.1)	38 (33.0)
Overactive and aggressive behaviour			
Not a problem	4,127 (64.9)	198 (62.3)	64 (59.3)
Minor problem	1,333 (21.0)	66 (20.8)	26 (24.0)
Significant problem	898 (14.1)	54 (16.9)	18 (16.7)

Non-accidental self-injury			
Not a problem	5,850 (92.1)	292 (91.8)	100 (92.6)
Minor problem	326 (5.1)	20 (6.3)	5 (4.6)
Significant problem	179 (2.8)	6 (1.9)	3 (2.8)
Cognitive problems			
Not a problem	3,799 (59.9)	181 (57.3)	64 (59.8)
Minor problem	1,578 (24.9)	83 (26.3)	23 (21.5)
Significant problem	966 (15.2)	52 (16.4)	20 (18.7)
Physical illness or disability			
Not a problem	3,502 (55.2)	175 (55.0)	57 (52.8)
Minor problem	1,254 (19.8)	73 (23.0)	23 (21.3)
Significant problem	1,591 (25.0)	70 (22.0)	28 (25.9)
Hallucinations and delusions			
Not a problem	2,688 (42.3)	97 (30.5)	34 (31.5)
Minor problem	1,314 (20.7)	74 (23.3)	25 (23.1)
Significant problem	2,348 (37.0)	147 (46.2)	49 (45.4)
Problems with activities of daily living			
Not a problem	2,842 (44.8)	121 (38.2)	44 (41.1)
Minor problem	1,572(24.8)	86 (27.1)	28 (26.2)
Significant problem	1,934 (30.4)	110 (34.7)	35 (32.7)
Service use			
Days of inpatients stay in previous six months mean ±SD (range)	11.8 ±36.3 (0-184)	35.8 ±60.0 (0-184)	18.8 ±44.2 (0-184)
Days of outpatient contact in previous six months- mean ±SD (range)	9.4±13.9 (0-174)	12.5±15.1 (0-153)	12.2±20.1 (0-153)
Previous CTOs			
No	6,483 (94.6)	394 (88.8)	98 (85.2)
Yes	374 (5.4)	37 (11.2)	17 (14.8)
Number of antipsychotics used in the previous six months mean ±SD (range)	1.0±1.0 (0-8)	2.2±1.2 (0-7)	1.2±1.0 (0-6)
Previous clozapine use			
No	5,643 (82.3)	151 (45.6)	80 (69.6)
Yes	1,214 (17.7)	180 (54.4)	35 (30.4)
Previous LAI use			
No	4,405 (64.2)	167 (50.5)	52 (45.2)
Yes	2,452 (35.8)	164 (49.5)	63 (54.8)

* Antipsychotic polypharmacy lasting for six or more months

Table 6.2 describes the prevalence of FGAs and SGAs that were prescribed as part of antipsychotic polypharmacy. Two or more SGAs were most commonly co-prescribed. Of the newly initiated sample, 24.3% were receiving clozapine antipsychotic polypharmacy.

Table 6.2 Prevalence and distribution of long-term antipsychotic polypharmacy.

Types of antipsychotic polypharmacy	Antipsychotic polypharmacy (n=331)		Antipsychotic polypharmacy initiation (n=115)	
	n	% (95% CI)	n	% (95% CI)
First generation antipsychotics (FGA) only	9	2.7 (1.3- 5.1)	6	5.2 (1.9- 11.0)
Second generation antipsychotics (SGA) only	216	65.3 (59.9- 70.4)	62	53.9 (44.4- 63.2)
FGA+ SGA	106	32.0 (27.0- 37.3)	47	40.9 (31.8- 50.4)
Antipsychotic polypharmacy inclusive of FGA or SGA LAI[a]	72	21.8 (17.3- 26.2)	35	30.4 (21.9- 38.9)
Antipsychotic polypharmacy inclusive of clozapine [a]	165	49.9 (44.4- 55.3)	28	24.3 (16.4- 32.3)

[a] Categories overlap with antipsychotic polypharmacy by generation (FGA; SGA; FGA+SGA)

Table 6.3 summarises results from the unadjusted and adjusted logistic regression models, which examine the potential socio-demographic and socioeconomic predictors of newly prescribed antipsychotic polypharmacy. In the fully adjusted model, individuals in early adulthood (aged 16-35) were more likely to be initiated on antipsychotic polypharmacy than older adults (aged 56+) (OR=2.1, 95% CI: 1.1-3.7, p=0.016), whereas being in a relationship was associated with a reduced risk for antipsychotic polypharmacy initiation (OR=0.3, 95% CI: 0.1-0.9, p=0.043). Experiencing a high level of deprivation and more specifically being homeless was also associated with an increased risk for being newly initiated on long-term antipsychotic polypharmacy (OR=3.3, 95% CI: 1.1- 9.9, p=0031).

Table 6.3 Logistic regression analysis of socio-demographic and socioeconomic predictors of antipsychotic polypharmacy initiation.

	Crude OR (95% CI)	Adjusted OR* (95% CI)	Adjusted p-value
Age			
16-35	**2.6 (1.6- 4.5)**	**2.1 (1.1- 3.7)**	**p=0.016**
36-45	1.7 (0.9- 3.0)	1.4 (0.8- 2.6)	p=0.291
46-55	1.3 (0.7- 2.4)	1.1 (0.6- 2.1)	p=0.749
56+	Reference	Reference	
Gender			
Female	Reference	Reference	
Male	1.3 (0.9- 1.9)	1.1 (0.7- 1.7)	p=0.621
Ethnicity group			
White	Reference	Reference	
Black Caribbean	1.2 (0.7- 2.2)	1.1 (0.6- 2.1)	p=0.691
Black African	**1.8 (1.2- 2.8)**	1.4 (0.9- 2.3)	p=0.129
Other	1.3 (0.7- 2.3)	1.3 (0.7- 2.4)	p=0.403
Relationship status			
Not in a relationship	Reference	Reference	
In relationship	**0.3 (0.1- 0.7)**	**0.3 (0.1- 0.9)**	**p=0.043**
Employment status			
Not in paid employment	Reference	Reference	
In paid employment	0.3 (0.1- 1.4)	0.4 (0.1- 1.6)	p=0.181
Deprivation level			
Low level	Reference	Reference	
Medium level	1.6 (0.9- 2.6)	1.4 (0.9- 2.4)	p=0.164
High level	**1.7 (1.0- 2.8)**	1.5 (0.9- 2.5)	p=0.116
Homelessness	**4.7 (1.6- 13.9)**	**3.3 (1.1- 9.9)**	**p=0.031**

***** Models adjusted for all socio-demographic and socioeconomic factors

As described in Table 6.4, overall clinical symptoms, as measured by HoNOS administered closest to the start of follow-up, were not predictive of antipsychotic polypharmacy initiation, with the exception of significant problems with hallucinations and/or delusions (OR=1.6, 95% CI:1.0-2.5, p=0.048). In a sensitivity analysis, where the investigation was restricted to HoNOS scores obtained within the last year prior to the observation period, this association was not substantially changed in strength, although fell outside statistical significance (OR=1.5, 95% CI: 0.9-2.4, p=0.146).

Table 6.4 Logistic regression analysis of clinical predictors of antipsychotic polypharmacy initiation.

Predictors	Crude OR (95%CI)	Adjusted OR* (95% CI)	Adjusted p-value
Comorbid diagnosis Depression			
No	Reference	Reference	
Yes	0.8 (0.5- 1.1)	0.8 (0.6- 1.2)	p=0.286
Personality disorder			
No	Reference	Reference	
Yes	1.4 (0.9- 2.3)	1.2 (0.7- 2.0)	p=0.464
Substance use			
No	Reference	Reference	
Yes	1.2 (0.8- 1.8)	1.0 (0.6- 1.5)	p=0.873
Overactive and aggressive behaviour			
Not a problem	Reference	Reference	
Minor problem	1.3 (0.8- 2.0)	1.3 (0.8- 2.0)	p=0.331
Significant problem	1.3 (0.8- 2.2)	1.3 (0.8- 2.2)	p=0.339
Non-accidental self-injury			
Not a problem	Reference	Reference	
Minor problem	0.9 (0.4- 2.2)	0.9 (0.4- 2.2)	p=0.804
Significant problem	1.0 (0.3- 3.1)	0.9 (0.3- 3.0)	p=0.922
Cognitive problems			
Not a problem	Reference	Reference	
Minor problem	0.9 (0.5- 1.4)	0.9 (0.6- 1.5)	p=0.818
Significant problem	1.2 (0.7- 2.0)	1.4 (0.8- 2.3)	p=0.222
Physical illness or disability			
Not a problem	Reference	Reference	
Minor problem	1.1 (0.7- 1.8)	1.4 (0.9- 2.4)	p=0.159
Significant problem	1.1 (0.7- 1.7)	1.6 (0.9- 2.6)	p=0.064
Hallucinations and delusions			
Not a problem	Reference	Reference	
Minor problem	1.5 (0.9- 2.5)	1.5 (0.9- 2.5)	p=0.141
Significant problem	**1.7 (1.1- 2.6)**	**1.6 (1.0- 2.5)**	**p=0.048**
Problems with activities of daily living			
Not a problem	Reference	Reference	
Minor problem	1.2 (0.7- 1.9)	1.2 (0.7- 1.9)	p=0.506
Significant problem	1.2 (0.8- 1.8)	1.2 (0.8- 1.9)	p=0.414

* Models adjusted for all socio-demographic and socioeconomic factors

Table 6.5 summarises associations between newly prescribed antipsychotic polypharmacy and service use. I found that the risk of antipsychotic polypharmacy initiation increased with every additional day of outpatient contact (OR=1.0099, 95% CI: 1.0002-1.0197, p=0.045) received in the previous six months, even after adjusting for possible confounders. Similarly, having previously received a CTO (OR=2.6, 95% CI: 1.5-4.5, p<0.001), previous use of clozapine (OR=1.8, 95% CI: 1.2-2.7, p=0.006), and previous LAI use (OR=2.2, 95% CI: 1.5-3.2, p<0.001) were all associated with increased risk of being newly prescribed long-term antipsychotic polypharmacy in the fully adjusted models.

In total, 419 (6.7%) patients in the sample had been referred for SLAM services from other boroughs rather than being catchment area residents. A sensitivity analysis indicated that after restricting the analyses to patients residing in the SLAM catchment area, the magnitude and direction of ORs were similar for all associations; however some were no longer significant including being in a relationship (p=0.056), having problems with hallucinations and/or delusions (p=0.123) and outpatient contact in the previous 6 months (p=0.058). Also, after excluding patients from outside the catchment there were no longer any homeless people prescribed long-term antipsychotic polypharmacy; therefore an analysis of this variable was not possible.

Table 6.5 Logistic regression analysis of service use predictors of antipsychotic polypharmacy initiation.

	Crude OR (95% CI)	Adjusted OR* (95% CI)	Adjusted p-value
Days of inpatients stay in previous six months	**1.0 (1.00- 1.01)**	1.0 (0.9- 1.0)	p=0.309
Days of outpatient contact in previous six months	**1.0095 (1.0007- 1.0183)**	**1.0099 (1.0002-1.0197)**	**p=0.045**
Number of antipsychotics used in the previous six months	**1.2 (1.0- 1.4)**	1.1 (0.9- 1.3)	p=0.291
Previous CTOs			
No	Reference	Reference	
Yes	**3.1 (1.8- 5.2)**	**2.6 (1.5- 4.5)**	**p<0.001**
Previous Clozapine use			
No	Reference	Reference	
Yes	**2.1 (1.4- 3.1)**	**1.8 (1.2- 2.7)**	**p=0.006**
Previous LAI use			
No	Reference	Reference	
Yes	**2.2 (1.5- 3.2)**	**2.2 (1.5- 3.2)**	**p<0.001**

***** Models adjusted for all socio-demographic and socioeconomic factors

6.5 Discussion

The results indicate that age, socioeconomic circumstances, psychotic symptoms, prior outpatient contact, CTOs, prior clozapine and/or LAI use are significant, independent predictors of newly prescribed long-term antipsychotic polypharmacy.

The findings are in keeping with existing research (Mace & Taylor 2015) indicating that SLAM has a considerably lower prevalence of antipsychotic polypharmacy in comparison to a UK national sample and other US studies (Freudenreich & Goff 2002; Gallego et al. 2012). Considering service use measures, the results both confirm previous research and generate novel findings. For example, the results support previous research which has indicated that prior service use, such as more frequent outpatient contact (Ganguly et al. 2004; Kreyenbuhl et al. 2007), previous use of LAI, and clozapine (Ganguly et al. 2004), are associated with an increased risk for longer term antipsychotic polypharmacy (e.g. >60 days). Importantly, the findings further indicate that only a third of the patients initiated on antipsychotic polypharmacy had previously been trialled on clozapine. This has been previously suggested (Howes et al. 2012; Nielsen et al. 2012), and highlights that prescribing guidelines (i.e. that antipsychotic polypharmacy should only be considered after trials of two individual agents followed by clozapine) are not consistently applied in 'real world' practice. Contrary to some previous reports, I found no evidence to suggest that antipsychotic polypharmacy initiation is predicted by the number of days spent as an inpatient or number of antipsychotics used (Barbui et al. 2006; Ganguly et al.

2004; Morrato et al. 2007) in the previous six months. An important issue to bear in mind is that I specifically investigated antipsychotic polypharmacy initiation, while previous research has rarely been able to account for pre-existing antipsychotic polypharmacy use and thus has not been able to distinguish factors associated with its initiation from those associated with its continuation. Furthermore, it is important to consider service use predictors in the context of the service where they are examined. For example, in the UK, there has been a nationwide drive to reduce the number and duration of inpatient admissions. Therefore, it is possible that factors, which would have previously warranted an inpatient admission, are now possibly driving antipsychotic polypharmacy prescribing due to limited beds. Future studies may benefit from testing further whether antipsychotic polypharmacy is initiated in the community in order to prevent hospital admission. The results further suggest that factors such as prior history of CTOs (a proposed proxy for non-adherence) are associated with an increased risk for long-term antipsychotic polypharmacy, something that has not been previously investigated (Biancosino et al. 2005; Patel et al. 2011).

Experiencing significant hallucinations and/or delusions, as rated on the respective HoNOS sub-scale, emerged as the sole symptomatic predictor of long-term antipsychotic polypharmacy initiation. Previous research has detected no association between general psychopathology and long-term antipsychotic polypharmacy (Barbui et al. 2006); however, most studies of smaller inpatient samples (Biancosino et al. 2005; Centorrino et al. 2004; Centorrino et al. 2005) have indicated an association between antipsychotic

polypharmacy and positive symptoms. Lastly, despite some previous evidence indicating that comorbid diagnoses such as personality disorder (Ganguly et al. 2004) and depression (Kreyenbuhl et al. 2007) are associated with reduced likelihood of antipsychotic polypharmacy prescribing, I detected no such associations with antipsychotic polypharmacy initiation.

Of the demographic factors that I examined, I found a positive association between antipsychotic polypharmacy and younger age (Kreyenbuhl et al. 2007; Morrato et al. 2007; Suokas et al. 2012). There are several potential explanations. For example, it is possible that younger patients are seen as better able to tolerate side effects associated with antipsychotic polypharmacy (Alexopoulos et al. 2004; Shin et al. 2013) or that higher perceived risk (e.g. of violence) influences prescribing behaviour. Ethnic background and gender, in contrast to other studies (Ganguly et al. 2004; Kreyenbuhl et al. 2007; Suokas et al. 2012), were not significantly associated with antipsychotic polypharmacy. I found a potentially protective effect of being in a relationship (Kreyenbuhl et al. 2007; Santone et al. 2011), which could suggest that being able to sustain an intimate relationship may be seen as a marker for better functioning and less impairment. Deprivation level emerged as the sole socioeconomic factor that predicted initiating long-term antipsychotic polypharmacy. In contrast with previous research where the principal focus has been on employment status (Barbui et al. 2006; Biancosino et al. 2005; Santone et al. 2011), the study suggests that deprivation is potentially a more meaningful measure of socioeconomic status. It is possible that homelessness acts as a proxy for illness severity (Gaebel & Zielasek 2015);

however, this association is novel, and the role of socioeconomic features in general warrants further investigation.

This study had several strengths. Measuring predictors prior to antipsychotic polypharmacy initiation allowed us to separate the exposures and outcome, thereby reducing the influence of reverse causality. I also examined antipsychotic polypharmacy of at least six months duration, which is likely to have excluded cross-titration, although it is possible that some instances may have begun with this (e.g. where a cross-titration was commenced but not completed due to worsening symptoms, resulting in the observed antipsychotic polypharmacy). I explored multiple factors simultaneously as predictors and confounders, and used data from a large sample including both inpatients and outpatients. Finally, in common with most NHS Mental Health Trusts in the UK, SLAM is close to being a monopoly mental health care provider for its geographic catchment; therefore the sample is likely to be representative of patients seen by secondary care (Stewart et al. 2009).

There were several potential limitations. Despite adjusting for multiple confounders, it is possible that some residual confounding may have occurred. I was unable to measure factors such as duration of illness or stages of treatment as patients entered the observation period. In addition, I was unable to measure clinician-related factors such as prescriber experience of initiating antipsychotic polypharmacy and knowledge of side effects and adverse outcomes (Correll & Gallego 2012; Correll et al. 2011; Gee et al. 2014). In contrast to previous research where standardised symptomatic

assessments have been used (e.g. PANSS, BPRS), symptom assessment in this study was limited to individual HoNOS items, measured at one point in time. This scale has received some previous criticism with regards to its measurement of symptoms (Bebbington et al. 1999; Stein 1999), and I was only able to analyse a composite measure of psychotic symptoms. It is possible that true associations may have been concealed, and further research is required into the role of observed and recorded symptomatology in clinical decision-making. Finally, I was unable to establish reasons for not trialling patients on clozapine. It is possible that some patients may refuse clozapine initiation; therefore, what may seem as inappropriate initiation of antipsychotic polypharmacy may be the result of the latter being the only treatment option available.

I believe that the findings have several important clinical implications. Long-term antipsychotic polypharmacy prescribing is unlikely to be predicted by a single factor; rather, it is precipitated by a complex interplay between patient and wider environmental contexts, where clinical symptoms as well as service use such as previous treatment and contact with services may influence decision-making. Furthermore, the study highlights that there are certain patient groups, such as patients whose symptoms are resistant to treatment, that are at an increased risk for antipsychotic polypharmacy initiation. Although a proportion of patients prescribed antipsychotic polypharmacy do receive pharmacotherapy that is in line with current treatment guidelines (e.g. LAI and clozapine trials that precede antipsychotic polypharmacy initiation), a subgroup is offered antipsychotic polypharmacy sooner than recommended.

Future research would benefit from focusing further on patients that are inappropriately initiated on antipsychotic polypharmacy, as a long-term treatment plan. Identifying these groups could encourage clinicians to employ a broader range of interventions, including earlier trials of clozapine and/or alternative treatments to pharmacotherapy to reduce the risk of antipsychotic polypharmacy prescribing.

CHAPTER 7: ANTIPSYCHOTIC POLYPHARMACY PRESCRIBING AND RISK OF HOSPITAL READMISSIONS IN SECONDARY MENTAL HEALTH CARE

The content of this chapter has contributed to the following:

Giouliana Kadra, Robert Stewart, Hitesh Shetty, James H. MacCabe, Chin-Kuo Chang, Jad Kesserwani, David Taylor and Richard D. Hayes. (Submitted). Antipsychotic polypharmacy prescribing and risk for hospital readmission.

7.1 Abstract

Background: Despite the lack of empirical evidence to support its superiority over monotherapy, clinicians continue to prescribe antipsychotic polypharmacy. However, little is known about the risk of readmission of patients discharged from hospital on antipsychotic polypharmacy.

Methods: Using data from the SLAM case register, service users with SMI who were discharged between 1st January 2007 and 31th December 2014, were followed up for six months, to estimate their risk of hospital readmission. Patients were classified as either receiving monotherapy or polypharmacy at index discharge. Multivariable Cox regression models were constructed, adjusting for socio-demographic, socioeconomic, clinical and service use factors to examine the risk for readmission in relation to antipsychotic polypharmacy prescribing.

Results: I identified 5,523 adults with SMI who had been admitted at least once to SLAM, of whom 1,355 (24.5%) were readmitted into secondary mental health care within six months of the index discharge. Being discharged on antipsychotic polypharmacy was associated with a significantly increased risk of readmission, in comparison to patients discharged on monotherapy (HR=1.4, 95% CI: 1.2- 1.7, $p<0.001$). This association was maintained in the fully adjusted model and following several sensitivity analyses.

Conclusion: The results suggest that patients discharged on antipsychotic polypharmacy are more likely to be readmitted into hospital within six months in comparison to those discharged on monotherapy. This needs to be considered in treatment decisions and the reasons for the association clarified.

7.2 Background

An additional regular antipsychotic is frequently added to treatment [as opposed to *pro re nata (*PRN)] in inpatient settings to manage residual clinical symptoms following monotherapy (Centorrino et al. 2008; Taylor et al. 2002; Grech & Taylor 2012; Lelliott et al. 2002; Barnes & Paton 2011a). However, antipsychotic polypharmacy has not been found to be associated with more clinical improvement from the time of admission, to the point of discharge, in comparison to monotherapy (Centorrino et al. 2005; Centorrino et al. 2004; Biancosino et al. 2005), and little is currently known about the effectiveness of antipsychotic polypharmacy, once patients return to the community.

Hospital readmission rates are high amongst individuals with SMI (Weiden & Olfson 1995; Schennach et al. 2012), with the risk for rehospitalisation peaking in the first months after discharge (Bodén et al. 2011). Factors that have been associated with an increased risk for readmission are shorter hospital stays (Boaz et al. 2013); medication non-adherence (Weiden et al. 2004; Haddad et al. 2014) and comorbid substance use (Boaz et al. 2013).

Research examining predictors of antipsychotic polypharmacy has indicated that patients with higher inpatient and outpatient contact (Kadra et al. 2016; Ortiz et al. 2016; Centorrino et al. 2004; Faries et al. 2005; Ganguly et al. 2004; Kreyenbuhl et al. 2007; Morrato et al. 2007; Connolly & Taylor 2014a) and greater illness severity (Kadra et al. 2016; Correll & Gallego 2012) are at particular risk of receiving antipsychotic polypharmacy prescription. Furthermore, research has indicated that antipsychotic polypharmacy

treatment has been characterised by being less likely to prevent hospital admission and significantly worse clinical symptoms and functioning (Moilanen et al. 2016; Kreyenbuhl et al. 2007). However, research to date examining the clinical stability of patients discharged on antipsychotic polypharmacy has been sparse and findings are inconclusive (Correll et al. 2009). Evidence has been mainly derived from health insurance records, with findings indicating that the choice between antipsychotic polypharmacy or monotherapy has no effect on the risk for readmission (Boaz et al. 2013); and that antipsychotic polypharmacy is associated with lower hospital readmission in comparison to monotherapy (Katona et al. 2014). There has been sparse evidence to suggest that clozapine is associated with reduced rehospitalisation (Valevski et al. 2012; Nielsen et al. 2012; Gee et al. 2016), and clozapine augmentation is currently the only antipsychotic polypharmacy regimen that has some empirical support (Freudenreich & Goff 2002; Howes et al. 2012; Taylor et al. 2011), hence its acceptance as a third-line treatment for SMI (NCCMH 2010). However, it is unclear whether people receiving clozapine polypharmacy or non-clozapine polypharmacy differ in risk of readmission.

7.2.1 Aims and hypotheses

The aim of this study was to determine if there was an association between being discharged on antipsychotic polypharmacy and risk of readmission, in a large cohort using de-identified electronic health records. Furthermore, I set out to investigate if the inclusion of clozapine in antipsychotic polypharmacy

had an impact on this risk. I hypothesised that those discharged on antipsychotic polypharmacy would be at increased risk of hospital readmission compared to antipsychotic monotherapy. I further hypothesised that clozapine polypharmacy prescription will make no difference to the risk of readmission compared to clozapine monotherapy.

7.3 Methods

I carried out a cohort study using de-identified data from SLAM EHRs, collected retrospectively for the time period between 1st January 2007 and 31st December 2014. For further information on SLAM and CRIS please refer to Chapter 4 section 4.2.

7.3.1 Selection criteria and primary outcome

I identified all adults who had received a SMI diagnosis such as schizophrenia (ICD-10 code: F20.x), schizoaffective disorder (F25.x) or bipolar disorder (F31.x) between 1st January 2007 and 31st December 2014. I further identified all patients with at least one inpatient admission during the observation period (1st January 2007 and 31st December 2014) and who were residents in the boroughs of SLAM. Patients resident outside the local catchment area can be referred to SLAM services for specialist treatment, due to particularly severe or treatment-resistant symptoms. However, these patients return to their borough of residence following discharge, and therefore follow-up for readmission is not possible for this group. Therefore, this group was excluded. For patients with multiple admissions, I selected admissions that were followed by a discharge on clozapine either as a single antipsychotic or part of polypharmacy, otherwise the first recorded admission was used. This was based on previous evidence suggesting that clozapine is often under-prescribed in relation to other antipsychotics and to polypharmacy (Lochmann van Bennekom et al. 2013), so I sought to identify as many cases as possible to increase statistical power sufficient to carry out an analysis for this group. I

followed up all patients from the point of their index inpatient discharge for a six-month period to establish whether or not they were readmitted into secondary mental health care. Previous research indicates that the risk for readmission is highest in the 30 days after inpatient discharge (Boaz et al. 2013) and I reasoned that a six-month window would thus capture most readmissions. Readmissions data were derived from structured fields in CRIS. Follow-up stopped at the first hospital readmission, date of death, or 31st December 2014, whichever occurred first. Date of death within the observation window was traced for the entire cohort through routine nationwide mortality tracing linked to the electronic health record and carried out on a monthly basis (Chang et al. 2010; Perera et al. 2016).

7.3.2 Data Extraction

I extracted clinical information in the EHR through CRIS from structured and unstructured fields (see Chapter 4 section 4.4). For antipsychotic prescribing I also used information available from SLAM pharmacy records. I examined all antipsychotic drugs listed in the BNF (see Table 4.1 in Chapter 4). Antipsychotic medication data in free text was also extracted using a NLP information extraction application developed using GATE software (Cunningham et al. 2013; Cunningham 2002)(for further information on NLP and GATE see Chapter 4 section 4.4.3), a suite of tools that facilitates the use and development of NLP applications and features, and which has been used to derive a large volume of meta-data in CRIS for previous and current research (Perera et al. 2016). NLP applications take into account the linguistic

context when extracting data from free text, therefore offering a more sophisticated approach to extracting information than basic key word searches.

7.3.3 Exposures of interest and other covariates

I examined individual EHRs to ascertain whether patients were discharged on a single antipsychotic (i.e. monotherapy) or two or more antipsychotics (i.e. antipsychotic polypharmacy). Antipsychotic regimen was determined by a patient being prescribed the same antipsychotic/s during their inpatient stay and in the six weeks following their discharge. Six weeks was chosen as patients are often given medication to take home for a maximum of four weeks, therefore medication prescription and repeat prescriptions are most often mentioned in the clinical notes within that time. In addition, I extracted a number of socio-demographic, socioeconomic, clinical and service use features.

Data extraction for age, gender, ethnicity, relationship status, and social deprivation are described in detail in Chapter 4 section 4.8. Age was calculated at index discharge and a likelihood ratio test indicated that it was appropriate to use age as a continuous variable in the analysis [$x^2(2)=1.42$, $p=0.49$]. Clinical symptoms were evaluated through HoNOS (see Chapter 4 section 4.8), prioritising those completed on or before the index discharge date. In cases where a HoNOS at or prior to discharge was not available, I took the closest score available after the discharge date. I further ascertained

whether or not the patient had received a mental illness diagnosis due to alcohol (ICD 10: F10) or opioid use (ICD 10: F11) prior to the index discharge (for further details see Chapter 4 section 4.8). I extracted two measures of prior service use: 1) the number of days spent as an inpatient in the six months prior to the index discharge date; the variable was used as categorical, following a likelihood ratio test [$x^2(1)=11.97$, $p=0.001$]; and 2) the proportion of face-to-face contact received as an outpatient in the six months prior to the index discharge; the variable was used as categorical following a likelihood ratio test [$x^2(1)=4.77$, $p=0.029$].

7.3.4 Statistical Analysis

STATA 13 was used to conduct all statistical analyses. Sample characteristics were summarised by percentage of readmission for the total cohort and by antipsychotic group. Kaplan–Meier curves with a log-rank test were used to compare those who were prescribed antipsychotic polypharmacy and monotherapy in relation to readmission. Following checks of proportional hazards assumptions ($p=0.82$), Cox regression procedures were used to examine the associations between antipsychotic polypharmacy and risk of readmission.

Age, gender, ethnicity, relationship status, deprivation status, clinical symptoms (HoNOS), comorbid diagnoses and service use in the six months prior to the index discharge date were included as covariates in the multivariable analysis. I further conducted several sensitivity analyses to test

whether any possible associations between antipsychotic polypharmacy and hospital readmissions were maintained after removing factors that may have had an effect: 1) I excluded patients with prior history of CTOs and long-acting injectable (LAIs) antipsychotics use. The above are potential markers of non-adherence and therefore important to account for when considering medication use. 2) I restricted the analysis to all patients with a diagnosis of schizophrenia (F20) in order to test if the association was maintained for this group. 3) I excluded patients from the borough of Lewisham as they did not have SLAM pharmacy data (however they did have medication data from structured and free-text fields in PJS). 4) I excluded patients with HoNOS scores obtained after the index discharge. 5) I restricted the analysis to patients who had not been prescribed clozapine. 6) Lastly, to reduce the effect of confounding by indication, I used standard propensity score methods, where the propensity score was the probability of being placed on polypharmacy at index discharge where all the potential confounders described in Table 7.1 were included in the model. The propensity scores were then used as a covariate in place of all of the aforementioned confounders (e.g. socio-demographic, socioeconomic, clinical and service use) in the Cox model. Propensity score was further used to identify patients who were at risk of being prescribed monotherapy and polypharmacy at discharge. I then constructed a fully adjusted Cox model and restricted the analysis to patients with this restricted range of propensity scores. Finally, I carried out a fully adjusted Cox model, where patients on clozapine antipsychotic polypharmacy and non-clozapine polypharmacy were compared to patients on clozapine monotherapy on their risk of hospital readmission. In

this latter analysis, clozapine monotherapy was considered to be, clinically, the most meaningful reference group. Clozapine prescribing often involves a period of clinical discussion, physical and blood checks. Therefore, patients who are initiated on clozapine could be somewhat different to patients that have not been initiated on clozapine. Therefore, restricting this latter analysis to patients that have been prescribed clozapine also reduces confounding by indication.

7.4 Results

Figure 7.1 describes the selection process for the final sample. In total 14,389 patients were dropped as a result of either not being prescribed antipsychotics and/or not having an inpatient admission. I compared the distribution of gender across patients who entered the monotherapy, polypharmacy cohort and everyone else and there was no significant difference in the distribution of gender across the three groups $x2(2)= 2.85$, $p=0.241$. In total 5,523 individuals met the inclusion criteria for the study. Table 7.1 describes the characteristics of the total cohort. Twenty five per cent (n=1,355) of the sample were readmitted within six months post-discharge. In total, 15.0% (n=826) of patients were discharged on antipsychotic polypharmacy and 85 per cent (n=4,697) patients were discharged on monotherapy. Of these, 30.9% (n=255) and 23.4% (n=1,100) were readmitted respectively.

Figure 7.1 Sample selection process.

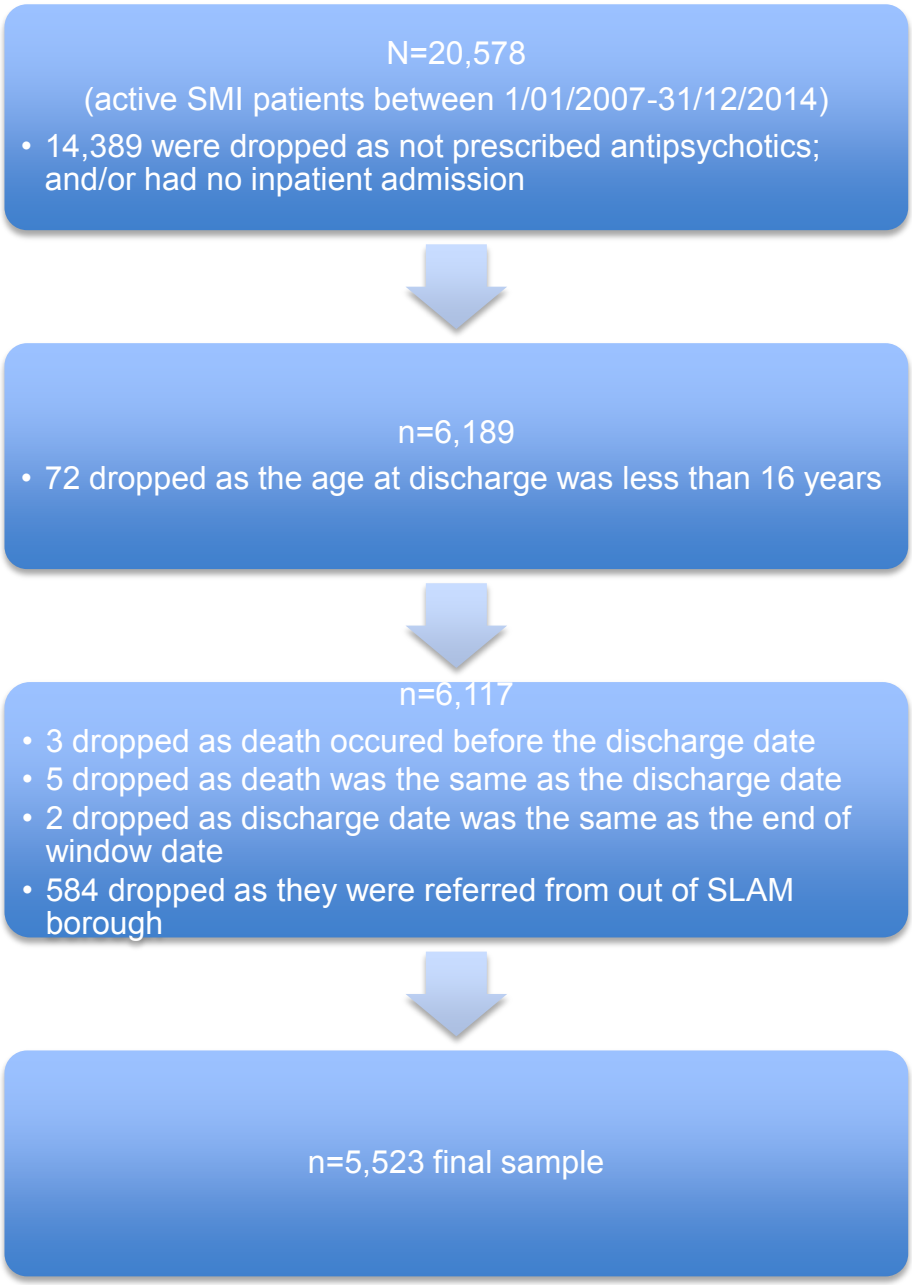


Table 7.1 Cohort characteristics.

Variables	Total sample n (%)
Total	5,523
Monotherapy	4,697 (85.0)
Antipsychotic polypharmacy	826 (15.0)
Socio-demographic and socioeconomic factors	
Age Mean (SD)	41.3 (14.5)
16- 34	2,052 (37.1)
35- 45	2,571 (46.6)
55+	900 (16.3)
Gender	
Female	2,573 (46.6)
Male	2,950 (53.4)
Ethnicity group	
British	1,662 (30.1)
Other White	453 (8.2)
Asian	334 (6.0)
Caribbean	730 (13.2)
African	1,926 (34.9)
Other	418 (7.6)
Relationship status	
No relationship	4,806 (87.0)
Relationship	717 (13.0)
Deprivation level in area of residence	
Low level	1,834 (33.2)
Medium level	1,844 (33.4)
High level	1,845 (33.4)
Clinical factors	
Diagnosis	
Schizophrenia (ICD-10: F20)	3,706 (67.1)
Schizoaffective disorder (ICD-10: F25)	490 (8.9)
Bipolar affective disorder (ICD-10:F31)	1,327 (24.0)
Overactive and aggressive behaviour	
Not a problem	3,081 (56.3)
Minor problem	1,222 (22.3)
Significant problem	1,166 (21.4)

Depressed Mood	
Not a problem	2,769 (50.7)
Minor problem	1,574 (28.8)
Significant problem	1,119 (20.5)
Non-accidental self-injury	
Not a problem	4,829 (88.3)
Minor problem	312 (5.7)
Significant problem	326 (6.0)
Physical illness or disability	
Not a problem	3,715 (68.1)
Minor problem	824 (15.1)
Significant problem	917 (16.8)
Hallucinations and delusions	
Not a problem	1,824 (33.4)
Minor problem	1,208 (22.1)
Significant problem	2,423 (44.5)
Problems with activities of daily living	
Not a problem	2,791 (51.5)
Minor problem	1,376 (25.4)
Significant problem	1,256 (23.1)
Problems with Living Conditions	
Not a problem	3,069 (57.9)
Minor problem	1,126 (21.2)
Significant problem	1,106 (20.9)
Problems with Occupation	
Not a problem	2,179 (41.1)
Minor problem	1,542 (29.1)
Significant problem	1,580 (29.8)
Problems with Relationships	
Not a problem	2,199 (40.6)
Minor problem	1,590 (29.4)
Significant problem	1,628 (30.0)
Prior alcohol use (ICD-10:F10)	
No	5,053 (91.5)
Yes	470 (8.5)
Prior opioid use (ICD-10:F11)	
No	5,442 (98.5)
Yes	81 (1.5)
Service use	
Days of inpatients stay in previous six months (tertiles)	
0-24 days	1,777 (32.2)
25-65 days	1,904 (34.5)

66-185 days	1,842 (33.3)
Days of outpatient contact in previous six months (tertiles)	
1-2 days	1,112 (27.2)
3-8 days	1,502 (36.7)
9-117 days	1,479 (36.1)

Characteristics of patients discharged on either monotherapy or polypharmacy are compared in Table 7.2. The two groups were very similar in their socio-demographic and socioeconomic characteristics. However, there was a higher proportion of white patients in the monotherapy group, whereas the polypharmacy group had a higher proportion of patients from black African and black Caribbean ethnic backgrounds. In addition, patients on monotherapy were more likely to have been diagnosed with bipolar affective disorder (ICD 10: F31), whereas patients prescribed polypharmacy were more likely to receive a schizophrenia diagnosis. Furthermore, patients discharged on antipsychotic polypharmacy were more likely to have significant problems with hallucinations and/or delusions, and had more contact with services in the previous six months, both inpatient and outpatient.

Table 7.2 Sample characteristics by antipsychotic regimen prescribed at index discharge.

Variables	Antipsychotic Monotherapy n (%)	Antipsychotic Polypharmacy n (%)	Test for significance
Socio-demographic and socioeconomic factors			
Age			
Mean (SD)	41.3 (14.7)	41.4 (13.1)	t(5521)=0.05, p=0.95
Gender			
Female	2,185 (46.5)	388 (47.0)	$X^2(1)=0.81$, p=0.58
Male	2,512 (53.5)	438 (53.0)	
Ethnicity group			
White	1,447 (30.8)	215 (26.0)	$X^2(5)=14.05$, p=0.02
Other White	383 (8.2)	70 (8.5)	
Asian	285 (6.1)	49 (5.9)	
Caribbean	596 (12.7)	134 (16.2)	
African	1,623 (34.6)	303 (36.7)	
Other	363 (7.7)	55 (6.7)	
Relationship status			
No relationship	4,083 (86.9)	723 (87.5)	$X^2(1)=0.23$, p=0.64
Relationship	614 (13.1)	103 (12.5)	
Deprivation level in area of residence			
Low level	1,548 (33.0)	286 (34.6)	$X^2(2)=1.29$, p=0.53
Medium level	1,581 (33.7)	263 (31.8)	
High level	1,568 (33.4)	277 (34.0)	
Clinical factors			
Diagnosis			
Schizophrenia (ICD-10: F20)	3,103 (66.1)	603 (73.0)	$X^2(2)=57.59$, p<0.001
Schizoaffective disorder (ICD-10: F25)	386 (8.2)	104 (12.6)	
Bipolar affective disorder (ICD-10:F31)	1,208 (25.7)	119 (14.4)	
Overactive and aggressive behaviour			
Not a problem	2,625 (56.4)	456 (55.8)	$X^2(2)=0.20$, p=0.90
Minor problem	1,039 (22.3)	183 (22.4)	
Significant problem	987 (21.2)	179 (21.9)	
Depressed Mood			
Not a problem	2,335 (50.3)	434 (53.2)	$X^2(2)=3.52$, p=0.17
Minor problem	1,341 (29.0)	233 (28.6)	
Significant problem	970 (20.9)	149 (18.3)	
Non-accidental self-injury			
Not a problem	4,105 (88.3)	724 (88.5)	$X^2(2)=4.05$,

Minor problem	257 (5.5)	55 (6.7)	p=0.13
Significant problem	287 (6.2)	39 (4.8)	
Physical illness or disability			
Not a problem	3,177 (68.5)	538 (65.9)	$X^2(2)=2.27$,
Minor problem	689 (14.9)	135 (16.5)	p=0.32
Significant problem	774 (16.7)	143 (17.5)	
Hallucinations and delusions			
Not a problem	1,609 (34.7)	215 (26.3)	$X^2(2)=23.52$,
Minor problem	1,023 (22.1)	185 (22.7)	p<0.001
Significant problem	2,008 (43.3)	415 (51.0)	
Problems with activities of daily living			
Not a problem	2,405 (52.1)	386 (47.7)	$X^2(2)=5.64$,
Minor problem	1,150 (24.9)	226 (27.9)	p=0.06
Significant problem	1,059 (23.0)	197 (24.4)	
Problems with Living Conditions			
Not a problem	2,559 (57.6)	470 (59.7)	$X^2(2)=2.15$,
Minor problem	974 (21.6)	152 (19.3)	p=0.34
Significant problem	941 (20.8)	165 (21.0)	
Problems with Occupation			
Not a problem	1,865 (41.3)	314 (39.8)	$X^2(2)=0.95$,
Minor problem	1,302 (28.9)	240 (30.4)	p=0.62
Significant problem	1,344 (29.8)	236 (29.9)	
Problems with Relationships			
Not a problem	1,883 (40.9)	316 (39.1)	$X^2(2)=1.04$,
Minor problem	1,343 (29.1)	247 (30.5)	p=0.59
Significant problem	1,382 (30.0)	246 (30.4)	
Prior alcohol use (ICD-10:F10)			
No	4,300 (91.5)	753 (91.2)	$X^2(1)=0.13$,
Yes	397 (8.5)	73 (8.8)	p=0.71
Prior opioid use (ICD-10:F11)			
No	4,624 (98.4)	818 (99.0)	$X^2(1)=1.67$,
Yes	73 (1.6)	8 (1.0)	p=0.19
Service use			
Days of inpatients stay in previous six months (tertiles)			
0-24 days	1,573 (34.5)	204 (24.7)	$X^2(2)=50.42$,
25-65 days	1,643 (35.0)	261 (31.6)	p<0.001

66-185 days	1,481 (31.5)	361 (43.7)	
Days of outpatient contact in previous six months (tertiles)			
1-2 days	979 (28.1)	133 (22.0)	$X^2(2)=19.12$,
3-8 days	1,294 (37.1)	208 (34.4)	$p<0.001$
9-117 days	1,215 (34.8)	264 (43.6)	

Figure 7.2. presents the Kaplan–Meier curves comparing readmission over time for patients discharged on either antipsychotic monotherapy or polypharmacy. Those prescribed monotherapy displayed significantly less readmission ($p < 0.001$) over time.

Figure 7.2 Kaplan-Meier survival curves displaying the readmission status of people with serious mental illnesses comparing those discharged on antipsychotic monotherapy to those discharged on polypharmacy (n=5,523)(p<0.001).

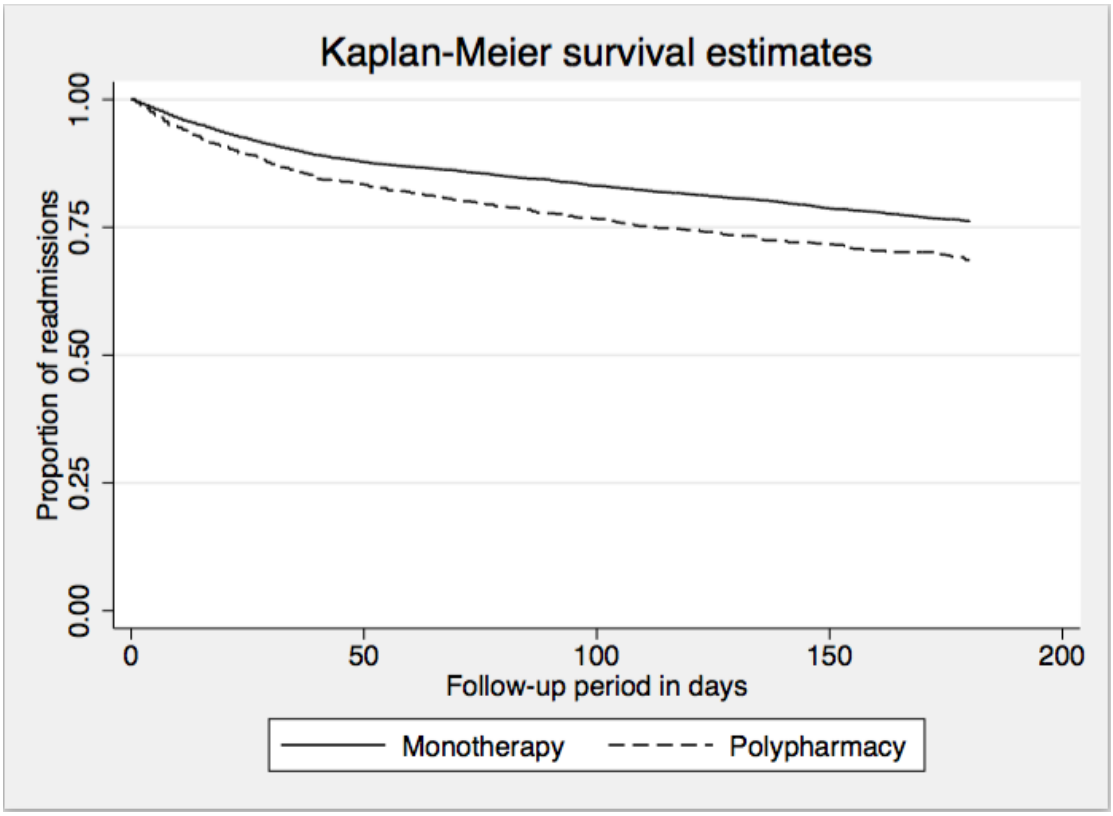


Table 7.3 summarises the Cox proportional hazards models of the associations between being discharged on antipsychotic polypharmacy and being readmitted into secondary mental health care. Antipsychotic polypharmacy was associated with a significantly increased risk for hospital readmission (adjusted HR=1.4, 95% CI: 1.2- 1.7, p<0.001), an association, which was sustained after adjusting for a number of socio-demographic, socioeconomic, clinical and service use factors. In addition, this association changed little after I further adjusted for propensity scores, in place of the above factors. I further conducted a number of sensitivity analyses, as described by Table 7.4, and restricted the analysis to patients who were at risk of being prescribed either monotherapy or polypharmacy (based on propensity scores). Patients with a propensity score ranging from 0.043 to 0.400 were considered to be at risk for both antipsychotic monotherapy and polypharmacy prescribing.

Table 7.3 Multivariable Cox regression analysis of the association between antipsychotic polypharmacy prescribing and hospital readmission in individuals with serious mental illnesses. (Monotherapy group is used as the reference group.)

N = 5,523 **Number of readmissions = 1,355** **Total person-time at risk (days) = 2,238** **Rate per 100 person-years = 60.53 (57.4-63.8)**		
Association between antipsychotic polypharmacy and hospital readmission	**Antipsychotic polypharmacy**	
	HR (95% CI)	**p value**
Unadjusted Model	**1.4 (1.2- 1.6)**	**p< 0.001**
Model adjusted for socio-demographic and socioeconomic factors	**1.4 (1.2- 1.6)**	**p< 0.001**
Model adjusted for clinical symptoms	**1.4 (1.3- 1.7)**	**p< 0.001**
Model adjusted for service use in previous 6 months	**1.3 (1.1- 1.6)**	**p< 0.001**
Model adjusted for all of the above factors	**1.4 (1.2- 1.7)**	**p< 0.001**
Model adjusted by using propensity score as a covariate	**1.4 (1.2- 1.7)**	**p< 0.001**

Table 7.4 Sensitivity analyses of the association between antipsychotic polypharmacy prescribing and hospital readmission in individuals with serious mental illness. (n=5,523 individuals; n=1,355 readmissions) (Monotherapy group is used as the reference group.)

Type of Antipsychotic Treatment	Antipsychotic polypharmacy	
	HR (95% CI)	**p value**
Analysis excluding patients on CTOs and previously prescribed LAI	**1.3 (1.1- 1.6)**	**p=0.006**
Analysis restricted to patients with ICD 10:F20 diagnosis	**1.5 (1.2- 1.8)**	**p< 0.001**
Analysis restricted to patients with ICD 10:F31 diagnosis	1.3 (0.9- 1.9)	p=0.224
Analysis excluding patients from the borough of Lewisham	**1.4 (1.2- 1.8)**	**p< 0.001**
Analysis excluding patients who have obtained their HoNOS score after the index antipsychotic prescription	**1.4 (1.2- 1.7)**	**p< 0.001**
Analysis restricted to patients who were at risk of being prescribed both monotherapy and polypharmacy (based on propensity scores)	**1.4 (1.2- 1.7)**	**p< 0.001**
Analysis restricted to patients without clozapine	**1.4 (1.1-1.6)**	**p=0.001**

Clozapine polypharmacy constituted four per cent of the sample (n=200), whereas non-clozapine polypharmacy was 11.3 per cent (n=626). A fully adjusted Cox proportional hazards model indicated that clozapine antipsychotic polypharmacy was associated with significantly increased risk for readmission in comparison to clozapine monotherapy (HR=1.8, 95% CI: 1.2-2.6, p=0.008) (Table 7.5). However, when I compared the risk for readmission between clozapine monotherapy and non-clozapine antipsychotic polypharmacy, I found no significant difference between the two regimens (HR=1.4, 95% CI: 0.9-1.9, p=0.063). As an additional analysis I also compared clozapine to non-clozapine polypharmacy. The results indicated no statistical difference between the two groups in relation to hospital readmission: fully adjusted HR=1.30 (0.89-1.89), p=0.170.

Table 7.5 Multivariable Cox regression analysis of the association between clozapine and non-clozapine antipsychotic polypharmacy prescribing and hospital readmission in individuals with serious mental illness. (n=1,221; readmissions=340)(clozapine monotherapy group has been used as a reference)

	Clozapine Polypharmacy (n=200)		Non-clozapine polypharmacy (n=626)	
Models	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Unadjusted Model	**1.6 (1.2- 2.2)**	**p= 0.004**	**1.6 (1.2- 2.0)**	**p<0.001**
Model adjusted for socio-demographic and socioeconomic factors	**1.6 (1.2- 2.3)**	**p=0.003**	**1.7 (1.3- 2.2)**	**p<0.001**
Model adjusted for clinical symptoms	**1.7 (1.2- 2.4)**	**p=0.003**	**1.5 (1.1- 1.9)**	**p=0.004**
Model adjusted for service use in previous 6 months	**1.6 (1.1- 2.4)**	**p=0.012**	**1.4 (1.0- 1.9)**	**p=0.031**
Fully[a] adjusted model	**1.8 (1.2- 2.6)**	**p= 0.008**	1.4 (0.9- 1.9)	p=0.063

[a] adjusted for all socio-demographic, socioeconomic, clinical and service use factors described in Table 7.1.

7.5 Discussion

This study examined the association between being discharged on antipsychotic polypharmacy from inpatient settings and subsequent mental health care readmissions in a retrospective analysis of a large cohort of patients, taking into account a wide range of other covariates. In summary, I found that patients discharged on antipsychotic polypharmacy were at an increased risk of re-hospitalisation. This association remained statistically significant and relatively unaltered in strength after multiple adjustments, sensitivity analyses and the use of propensity score methods to address confounding by indication. The results further indicated that patients discharged on clozapine polypharmacy had a greater risk for readmission when compared to patients on clozapine monotherapy.

Previous research on antipsychotic polypharmacy as a predictor of readmission has been sparse and inconclusive. My findings were consistent with evidence from clinical records studies (Moilanen et al. 2016; Kreyenbuhl et al. 2007; Kreyenbuhl et al. 2007), indicating that patients prescribed antipsychotic polypharmacy were more likely to be admitted to secondary mental health care inpatient settings. For example, Kreyenbuhl and colleagues (Kreyenbuhl et al. 2007) found that patients who had an additional antipsychotic prescribed, as opposed to being switched to a different antipsychotic, were three times more likely to be hospitalised. However, my findings were not in agreement with previous research investigating medical insurance records and rehospitalisation amongst patients prescribed long-term antipsychotic polypharmacy (Boaz et al. 2013; Katona et al. 2014). For

example, Boaz and colleagues (Boaz et al. 2013) found that polypharmacy at discharge was not associated with future hospital readmissions; rather readmission was associated with patients being insufficiently stable at the point of initial discharge. Greater clinical severity in patients prescribed antipsychotic polypharmacy is one possible mechanism proposed to explain the higher level of readmission, and is consistent with the associations I found for antipsychotic polypharmacy at discharge with schizophrenia diagnosis, positive symptoms, and higher service contact (Kadra et al. 2016; Correll & Gallego 2012; Centorrino et al. 2004; Faries et al. 2005; Ganguly et al. 2004; Kreyenbuhl et al. 2007; Morrato et al. 2007). However, the association with readmission persisted and was largely unaltered after adjusting for these factors. Adjusting for other factors known to affect levels of readmission such as possible medication non-adherence (Weiden et al. 2004; Haddad et al. 2014) as indicated by previous CTOs and LAI prescription, and substance use (Boaz et al. 2013), also made little difference to the results. Furthermore, the association between polypharmacy and readmission was sustained after restricting the analysis to patients who potentially might have been prescribed antipsychotic monotherapy or polypharmacy based on their propensity scores. This would suggest that patients discharged on antipsychotic polypharmacy are at a particular risk of readmission even after controlling for their personal and symptom characteristics by adjusting for these in the models. I found no evidence to suggest that antipsychotic polypharmacy (whether this was clozapine or non-clozapine) was associated with a lower risk for readmission, as indicated by Katona and colleagues (Katona et al. 2014). An important caveat to consider is that both of the aforementioned studies have considered

medical insurance population. Therefore, it is likely that differences in results are partly due to differences in the populations that were examined. For example, in the US patients that can pay for health care can be inherently different to patients that cannot afford private health care. Furthermore, despite general consensus across countries with regard to treatment guidelines (APA 2010; NICE & NCCMH 2013), it is possible that clinical practices does differ, and the aforementioned evidence reflects true prescribing differences across countries.

Contrary to my hypothesis that clozapine polypharmacy would have no effect on the risk for readmission, the results indicated that this risk was significantly higher for this group as compared to clozapine monotherapy. The same pattern was not observed for patients on non-clozapine polypharmacy. Existing research, mainly based on randomised controlled trials and open label trials, examining clozapine polypharmacy has indicated little to no benefit of this regimen (Freudenreich & Goff 2002; Taylor et al. 2011; Galling et al. 2017). However, there has been a general lack of previous research examining this treatment regimen in relation to readmission in large observational cohort studies that are representative of real-life clinical practice. The latter findings are important for another reason. The evidence suggests that within the groups of patients receiving antipsychotic polypharmacy, there could be a sub-population that is at a particularly high risk for readmission. This could be due to a number of different factors (such as severity of clinical symptoms), which need further investigation.

7.5.1 Strengths

This study had several strengths. SLAM, in common with other UK secondary mental health services, is a near-monopoly provider for its geographic catchment (Stewart et al. 2009; Perera et al. 2016), increasing the potential generalizability of findings and maximising their reflection of real-world clinical practice (Stewart et al. 2009). In addition, the large cohort provided statistical power to detect the primary association of interest and to adjust for broad range of potential confounders. All exposures were measured on or before the index discharge, therefore enabling us to make temporal inference with regards to antipsychotic polypharmacy and readmission.

7.5.2 Limitations

There were several potential limitations in this study, which need to be borne in mind. Despite multiple adjustments, residual confounding cannot be excluded absolutely in an observational design. Specifically, I did not capture factors such as duration of prior hospital admissions (Bodén et al. 2011; Boaz et al. 2013). In addition, as I did not measure the length of the antipsychotic regimen prescription after discharge, beyond looking for medication prescription within the first six weeks post discharge to confirm the regimen, it is possible that risk of readmission varies by length of medication prescription (e.g. short term verses long-term medication prescribing). Further research would benefit from examining differences in risk of readmission by length of antipsychotic regimen prescription. Symptom assessment in this study was limited to individual HoNOS items, measured at one point in time. This scale

has received some previous criticism with regards to its measurement of symptoms (Bebbington et al. 1999; Stein 1999), and I was only able to analyse a composite measure of clinical symptoms and daily functioning. Although I employed propensity score adjustment and restriction, confounding by indication cannot be completely ruled out.

7.5.3 Implications

The findings of this study have several important implications. The high level of inpatient readmission can be interpreted as an indicator that antipsychotic polypharmacy is not effective in managing mental health symptoms in the community. The results further indicated that patients on antipsychotic polypharmacy are generally more unwell, therefore the prescription of regimens that lack empirical support are likely to further increase patient burden already present in this population (Kreyenbuhl et al. 2007; Gallego et al. 2012; Waddington et al. 1998; Ganguly et al. 2004; Paton et al. 2008; Taylor et al. 2000). I found that patients receiving clozapine polypharmacy had a particularly elevated risk for readmission as compared to clozapine monotherapy. This is suggestive of potential difference in treatment needs across patients receiving antipsychotic polypharmacy, and further indicating this is not a homogeneous population. Therefore, future research would benefit from further examining this sub-group in relation to their clinical symptoms, treatment needs and course of antipsychotic medication prescribing (e.g. time from non-clozapine monotherapy to clozapine augmentation). Lastly, the findings provide further support for the need to

reduce antipsychotic polypharmacy prescribing. Antipsychotic polypharmacy prescribing has remained widespread not only across clinical services but also across countries and time (Gallego et al. 2012), with a trend that has been resistant to change (Paton et al. 2008) and with a high cost to service. More specifically, antipsychotic polypharmacy has been associated with a higher bed occupancy and length of inpatient stay, in addition to extra cost associated with multiple medication prescribing (Baandrup et al. 2012; Gilmer et al. 2007; Valuck et al. 2007). Evidence from a recent quality improvement programme has indicated that polypharmacy can be reduced successfully (Mace & Taylor 2015). Therefore, there is a clear need for similar programmes to be implemented on a wider national level.

CHAPTER 8: LONG-TERM ANTIPSYCHOTIC POLYPHARMACY PRESCRIBING IN SECONDARY MENTAL HEALTH CARE AND THE RISK OF DEATH

The content of this chapter has contributed to the following:

Giouliana Kadra, Robert Stewart, Hitesh Shetty, James H. MacCabe, Chin-Kuo Chang, David Taylor and Richard D. Hayes. (Submitted). Long-term antipsychotic polypharmacy prescribing in secondary mental health care and risk of mortality.

8.1 Abstract

Background: This study has addressed a recent call for research to examine the risk of mortality for patients prescribed regular long-term antipsychotic polypharmacy. Existing evidence has been hampered by several methodological problems, such as problems with the measurement of antipsychotic polypharmacy and residual confounding.

Methods: Using data from the South London and Maudsley (SLAM) anonymised case register (CRIS), I identified all adult patients with serious mental illness (SMI) who had been prescribed a single antipsychotic or polypharmacy, for six or more months between 2007 and 2014. Data on all-cause and cause-specific mortality were extracted using existing linkages between CRIS and death certification (Office of National Statistics). Multivariable Cox regression models were constructed, adjusting for socio-demographic, socioeconomic, clinical factors and smoking, to examine the association between antipsychotic polypharmacy prescribing and the risk for death.

Results: I ascertained 10,945 adults with SMI who had been prescribed long-term antipsychotic monotherapy (76.9%) or polypharmacy (23.1%). In total, 920 deaths occurred in the observation period. Patients on long-term antipsychotic polypharmacy had a small, elevated relative risk of mortality, which was significant in some, but not all models. The adjusted hazard ratios for death from natural and unnatural causes associated with antipsychotic polypharmacy were 1.2 (95% CI: 0.9-1.4, p=0.111) and 1.1 (95% CI: 0.7-1.9, p=0.619) respectively. The strength of the associations between

antipsychotic polypharmacy and mortality outcomes were similar after adjusting for antipsychotic dose or other potential confounders.

Conclusion: I found insufficient evidence to indicate that long-term antipsychotic polypharmacy is associated with a significantly elevated risk of death in comparison to patients prescribed antipsychotic monotherapy.

8.2 Background

Patients with SMI have been estimated to die approximately 15 to 20 years earlier than the general population (Chang et al. 2011; Brown et al. 2000; Auquier et al. 2006). Although suicide, accidents, violence and poor lifestyle choices such as smoking (Goff et al 2005; Auquier et al. 2006; Osborn et al. 2014) partially explain some of this mortality gap, the underlying factors remain unclear.

8.2.1 Antipsychotic medications

The prescribing of antipsychotic medications to individuals with SMI has been questioned as a possible contributing factor to premature death in this population. Although research has been sparse, there is some evidence to suggest that FGAs are associated with a higher mortality rate from natural causes and suicide (Kiviniemi et al. 2013; Joukama et al. 2006). Research examining SGAs has been more ambiguous. For further details see Chapter 1 section 1.2.

8.2.2 Antipsychotic polypharmacy

Antipsychotic medications, and more specifically the widespread prescribing of medication regimens not recommended by existing guidelines (NICE & NCCMH 2013; APA 2010), such as antipsychotic polypharmacy, are believed to significantly contribute to this increased mortality (Waddington et al. 1998; Joukama et al. 2006) observed in patients with SMI. Furthermore, this risk has been reported to increase if the dose prescribed is high, especially when

exceeding national recommendations (e.g. BNF)(Barbui et al. 2016; Connolly & Taylor 2016; Moilanen et al. 2016; Torniainen et al. 2015; Ray et al. 2009; Osborn et al. 2014). This literature has been reviewed and discussed in detail in Chapter 2. Briefly, there have been considerable differences in findings between studies examining long-term and unspecified antipsychotic polypharmacy duration (Waddington et al. 1998; Joukama et al. 2006; Baandrup et al. 2010; Katona et al. 2014). Therefore, it is possible that discrepancies have been due to methodological differences in measuring antipsychotic polypharmacy. Furthermore, studies that have detected an increased risk for death have examined smaller and/or specific groups in the population such as inpatients, possibly limiting the generalizability of their findings (Waddington et al. 1998; Joukama et al. 2006). Conversely, some studies that have found no effect of polypharmacy on death, have examined a limited number of potential confounders (Tiihonen et al. 2012), such as antipsychotic dose, therefore risking residual confounding. There is some evidence indicating that patients prescribed antipsychotic polypharmacy are more likely to be prescribed a higher combined dose of antipsychotics in comparison with patients on antipsychotic monotherapy (Roh et al. 2013). The receipt of high antipsychotic dose has in turn been associated with increased risk for death and more specifically mortality from cardiovascular and stroke causes (Osborn et al. 2014). In fact, some research has argued that the risk of death in SMI patients is associated with antipsychotic dose rather than antipsychotic regimen (Torniainen et al. 2014), where patients exposed to no antipsychotics and to high antipsychotic doses are at a particularly increased risk of dying.

Consequently the effect of antipsychotic polypharmacy on serious outcomes such as death remains unclear. Several recent papers have called for further research in this field (Grech & Taylor 2012; Kreyenbuhl et al. 2006), given that polypharmacy prescribing remains persistently common in clinical practice, despite guidelines explicitly advocating against its use. Furthermore, programmes that have aimed to reduce its prevalence have had limited success (Paton et al. 2008). Therefore, findings in this field could have important treatment implications at individual and service levels.

8.2.3 Aims and hypotheses

The aim of this study was to determine if there was an association between long-term use of antipsychotic polypharmacy and risk of death, in a large cohort using de-identified EHRs. Furthermore, I set out to investigate whether this risk varies depending on the cause of death and other factors such as antipsychotic dose. I hypothesised that patients receiving long-term antipsychotic polypharmacy would be at increased risk of all-cause mortality, in comparison to patients on long-term monotherapy. I further expected that the risk for death will be greater for natural causes of death and for patients on a higher dose of combined antipsychotics. In addition, I investigated whether patients on higher doses are at increased risk of death and the extent to which this accounted for any associations with antipsychotic polypharmacy.

8.3 Methods

8.3.1 Study design and data source

This was a retrospective cohort study, which examined anonymised data from SLAM EHRs between 1st January 2007 and 31st December 2014. For further detail on CRIS and SLAM please refer to Chapter 4 section 4.2.

8.3.2 Study sample

Using CRIS, I ascertained all adult patients with a diagnosis of schizophrenia (ICD-10 code: F20.x), schizoaffective disorder (F25.x) or bipolar disorder (F31.x) and who were in contact with SLAM clinical services during the observation period between 1st January 2007 and 31st December 2014 (for further details see Chapter 4 section 4.6). In this study, I used a looser definition of 'active', where a first contact could be a telephone call. This was done in order to identify the very first time a patient became known to services. In the previous chapters 'active' was identified as the first attended event/ face-to-face contact.

8.3.3 Outcomes

Mortality data extraction is described in detail in Chapter 4 section 4.4.4. Exact date of death was extracted to determine all-cause mortality in the observation period. I further determined the primary cause of death for each patient (cause-specific mortality). Causes of death were categorised into two

groups. Unnatural death included the following ICD10 diagnostic codes recorded on the death certificate: S00-T98 (injury, poisoning and certain other consequences of external causes); V01-Y98 (external causes of morbidity and mortality); and U509 (death from injury or poisoning, or event awaiting determination). All other codes were classified as natural causes of death. Cause-specific mortality data were extracted using a CRIS linkage with death records held by the Office of National Statistics (ONS), a process whereby anonymised BRC IDs are linked to the death register (Perera et al. 2016)(for further details please refer to Chapter 4 section 4.4.4).

8.3.4 Exposures of interest

Antipsychotic medication data were extracted from the SLAM pharmacy-dispensing database, and from structured and free-text fields in CRIS (see Chapter 4 section 4.4 for description). All antipsychotic medications listed in the BNF65 were considered (see Chapter 4, Table 4.1). A long-term antipsychotic polypharmacy episode was defined as the first record of concurrent prescription of two or more antipsychotics for six or more months, in the observation window (also referred to as the index polypharmacy date). A detailed description of how antipsychotic polypharmacy was derived is provided in Chapter 5 section 5.3.4. The first recorded episode of antipsychotic polypharmacy was selected in order to minimise previous antipsychotic polypharmacy episodes having an effect on the outcome of interest. The 1st January 2007 was selected as the point at which I began searching for a polypharmacy episode, due to having more complete EHRs

from this point onwards. If an antipsychotic polypharmacy episode was not recorded, I looked for the first episode of antipsychotic monotherapy in the observation period: where a patient was prescribed a single antipsychotic for six or more months (also referred to as the index monotherapy date). I considered several other possible reference groups (discussed in detail in the section 8.4.4 of this chapter); however, selecting the first episode of monotherapy maximised the time available for follow-up, thus limiting the possibility for potential biases in relation to follow-up.

For each patient, the follow-up time commenced at the point they were receiving antipsychotic polypharmacy or monotherapy for six or more months (index date). Follow-up continued until a death was recorded or the end of the observation period (31st December 2014), whichever occurred first.

8.3.5 Validation

The validation process is described in more detail in Chapter 4 section 4.7.1. I validated the performance of the algorithm described in Chapter 5, to ensure it was working well for this specific cohort. I conducted a manual examination of clinical notes for 35 patients who were identified as receiving long-term antipsychotic polypharmacy. I detected a positive predictive value (PPV) (i.e. precision) of 0.8. I further examined 17 cases identified as long-term monotherapy and detected a PPV of 0.9. Sensitivity (recall) was calculated as 0.8 after examining a random set of 20 cases including both antipsychotic monotherapy and polypharmacy.

8.3.6 Antipsychotic dose

Information on antipsychotic dose value, unit and frequency was extracted from free text, using NLP and structured fields, for both monotherapy and polypharmacy, where such information was available. Antipsychotic polypharmacy cases, where dose was not available for all antipsychotics that were part of the polypharmacy, were not included in the analysis. I manually validated prescribed daily dose by examining 43 randomly selected patients from the cohort. Positive predictive value (i.e. precision) was observed to be 0.8.

I used two different methods to calculate dose equivalents. Percentage out of maximum BNF recommended dose is currently recommended by the Royal College of Psychiatrists (Royal College of Psychiatrists 2014) as one of the preferred approaches to identify high-dose prescribing. However, this approach does not take into account the fact that efficacy for some antipsychotics takes place at lower doses (Connolly & Taylor 2014b), therefore creating a clustering towards lower values when converting overall dose into a percentage. I therefore used olanzapine equivalence (Gardner et al. 2010) as an alternative approach, which has been favoured by recent publications in antipsychotic polypharmacy (Patel et al. 2013; Gisev et al. 2014).

Percentage BNF dose (%BNF)

This was calculated by converting the dose of each drug into a percentage of the BNF (%BNF) maximum recommended dose for that drug. For polypharmacy, the percentages for individual antipsychotics were added together into a summed value. A cumulative dose of more than 100% was considered a high dose (Royal College of Psychiatrists 2014).

Information regarding the maximum recommended doses for individual antipsychotics was derived from the BNF 65 (British National Formulary 2015). Seven antipsychotics have an oral and depot form. Therefore, I created several rules to calculate the dose for these specific medications, in order to distinguish between the two forms of the same antipsychotic. In the first instance, where an initiation dose for depot was available, I used it to specify that any instance where the patient was prescribed a dose equal or above this value would be considered as depot, whereas doses lower than the depot initiation dose would be considered as oral. In cases where the depot initiation dose and the maximum oral dose were very close in value, I used the usual maintenance dose for depot to distinguish from oral prescriptions. This is described in Table 8.1. The maximum dose for oral and depot, respectively, were used to calculate the final percentage BNF dose. A likelihood ratio test indicated that it was appropriate to use this as a continuous variable in the analysis (p=0.056).

Table 8.1 BNF recommended antipsychotic dose.

Antipsychotic	Max Oral Dose Value	Reference value*	Depot initiation dose	Depot maintenance dose	Depot maximum dose
Amisulpride	1200				
Aripiprazole	30	200		300	400
Asenapine	20				
Benperidol	1.5				
Chlorpromazine	1000				
Clozapine	900				
Flupentixol	18	50	20	50	400
Fluphenazine	n/a		12.5	12.5	100
Haloperidol	20	50	25	50	300
Levomepromazine	1000				
Olanzapine	20	50		150	300
Paliperidone	12	25	25	50-150	150
Pericyazine	300				
Perphenazine	24				
Pimozide	20				
Pipotiazine	n/a		25	50-200	200
Prochlorperazine	100				
Quetiapine	750				
Risperidone	16	25	25	25-50	50
Sulpiride	2400				
Trifluoperazine	40				
Ziprasidone	200				
Zuclopenthixol	150	200	100	200	600

*Dose value used as a reference to distinguish between depot and oral form of administration of the same antipsychotic

Olanzapine equivalence dose

An alternative method to comparing dose across antipsychotics is to convert each into an olanzapine equivalent dose. To achieve this I used the Gardner et al. (Gardner et al. 2010) consensus method, which has been applied in several previous studies (Gisev et al. 2014; Patel et al. 2013). Polypharmacy doses were calculated by adding up the equivalence doses of all antipsychotics that were part of the polypharmacy regimen. A total dose above 20 milligrams (mg) was classified a high dose, based on previous research in this field (Gardner et al. 2010; Gisev et al. 2014; Patel et al. 2013). A likelihood ratio test indicated that it was most appropriate to use this variable as categorical (p=0.002), where 1-10mg was identified as a low dose, 11-20mg as medium dose and 21mg or above as high dose. Due to no previous published information on olanzapine equivalence for asenapine, I was unable to generate an olanzapine equivalence conversion, resulting in dropping a total of five cases for this specific analysis.

8.3.7 Covariates

Age, gender, ethnicity, and relationship status were derived from structured fields, closest to the index date. A likelihood ratio test indicated that it was appropriate to use age as a continuous variable in the analysis (p=1.000). Ethnicity, relationship status, employment and deprivation level data extraction and classification are detailed in Chapter 4, section 4.8.

Clinical factors included the patient receiving a comorbid diagnoses of depression (ICD-10: F32, F33); personality disorder (ICD-10: F10-16); substance use (ICD-10: F60; F61), prior to or at the point follow-up began. I ascertained this using information available from free text and structured fields. In addition, I identified the lengths of time, in days, each patient was known to SLAM services at the index date, by examining all structured and free-text records available since 1st January 2007 up until the point the patient qualified for antipsychotic polypharmacy or monotherapy group. A likelihood ratio test indicated that it was appropriate to use this variable as a continuous in the analysis (p=0.597). The extraction and coding of these variables is described in Chapter 4 section 4.8.

Given the increased risk of death amongst smokers (Goff et al. 2005; Dickerson et al. 2013), patients were classified in two groups, those who have never smoked and those who have in the past or are currently smoking (further details on classification are described Chapter 4 section 4.4.3).

8.3.8 Statistical analysis

STATA 13 was used to conduct all statistical analyses. Sample characteristics were summarised for the total cohort, as well as for all those who were in the long-term antipsychotic polypharmacy and monotherapy group. Cox proportional hazard models were used to determine whether any of the socio-demographic, socioeconomic or clinical factors were significantly associated with all-cause mortality. I further used chi-square tests to investigate whether

the monotherapy and polypharmacy group differed in relation to their sample characteristics. Kaplan–Meier curves with a log-rank test were used to compare those who were prescribed antipsychotic polypharmacy and monotherapy in relation to all-cause mortality. Following checks of proportional hazards assumptions [$x^2(2)=2.12$, $p=0.346$], Cox regression procedures were used to examine the associations between antipsychotic regimen and risk of death.

Multivariable models included potential confounders such as age, gender, ethnicity, relationship status, deprivation status, comorbid diagnoses (depression; personality disorder, and substance use), time known to SLAM and smoking. Two additional fully adjusted models including percentage BNF and olanzapine equivalence dose, respectively, were also run. To reduce the effect of confounding by indication, I used a standard propensity score methods, where the propensity score was the probability of being placed on polypharmacy at index discharge based on all variables described above (aside from dose). Dose was not included in calculating the propensity score due to not having available dose information for all patients in the cohort. The propensity scores were then used as a covariate in place of all of the aforementioned confounders in the Cox model. In addition, the following sensitivity analysis were planned to test whether any associations between polypharmacy and all-cause mortality were maintained after removing particular subgroups: 1) I restricted the analysis to patients who had not been prescribed clozapine, following evidence that clozapine could reduce the risk of death (Hayes et al. 2014); 2) I restricted the analysis to all patients who

had a FGA as part of their treatment regimen. FGAs have previously been associated with an increased risk of death (Kiviniemi et al. 2013; Joukama et al. 2006); 3) I excluded all patients who came from outside the four catchment boroughs. Patients resident outside the local catchment area can be referred to SLAM services for specialist treatment, due to particularly severe or treatment-resistant symptoms. Therefore, this group could be inherently different to local patients; 4) Lastly, standard propensity score methods were used to restrict the analysis only to patients who were at risk of both monotherapy and polypharmacy prescribing, based on their propensity scores. More specifically, this was achieved by removing patients from the analysis who, based on their propensity score, could have only been prescribed antipsychotic monotherapy or polypharmacy. In addition, separate Cox models were built to test the association between all-cause mortality and prescribed dose. However, Cox regression does not allow for the occurrence of two competing risks (i.e. different causes of death). Therefore, to examine the risk for cause-specific mortality, I used competing risk regression analyses, which allows for more than one competing risk in the cohort. Competing risk regression focuses on the cumulative incidence function, which indicates the probability of the event happening before a given time. Chi-square test was used to compare the sample characteristics between natural and unnatural groups of death.

8.4 Results

I identified 21,398 patients with SMI active in SLAM services during the eight-year follow up. Out of those 10,945 individuals met the inclusion criteria for the study. Figure 8.1, illustrates the sample selection process for this study. I compared the individuals from the final cohort (n=10,945) to those who were not prescribed a long-term antipsychotic regimen (i.e. everyone else) (n=9,422) in relation to their gender and age. Patient prescribed a long-term antipsychotic regimen were older [long-term antipsychotic regimen (Mean= 41.2, SD=15.1) and everyone else (M= 40.6, SD= 16.4), ttest (df=20367)= -2.995, p=0.0027] and more likely to be male [56.2% as compared to 51.6% in the everyone else sample, x^2(df=1)=44.39, p<0.001]. The mean time of follow up was 1636 days (standard deviation= 839), which is approximately four and a half years.

Figure 8.1 Sample selection process.

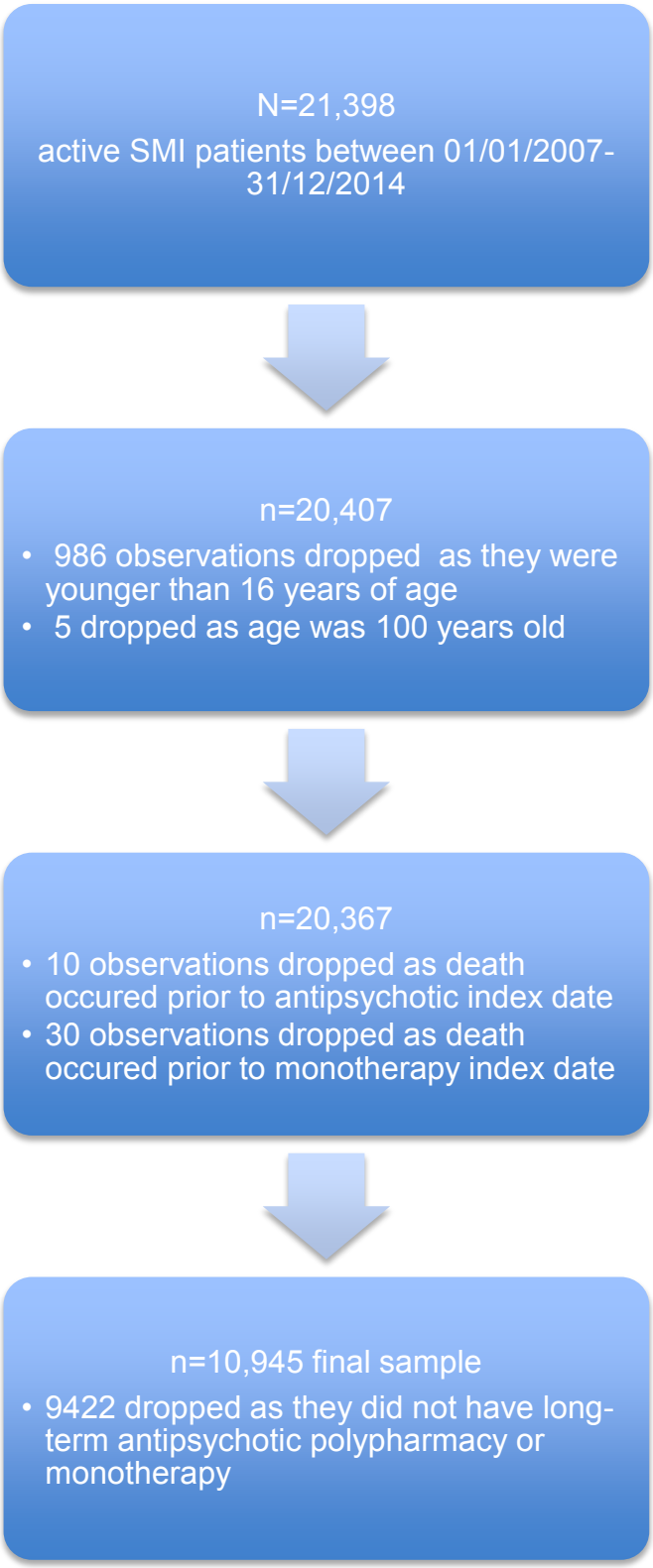


Table 8.2 describes the characteristics of the total cohort, together with an age and gender adjusted Cox regression analysis of the associations between death and sample characteristics. In total, 920 (8.4%) patients died within the observation window. Age, gender, comorbid substance use and having ever smoked were all associated with an increased risk for all-cause mortality, whereas being in a relationship at the time the follow-up began or being of black African or Caribbean ethnicity was associated with a lower risk for death.

Table 8.2 Cox regression analysis of the association between sample characteristics and mortality.

N = 10,945 **Number of deaths = 920** **Total person-time at risk (years) =49,026** **Rate per 100 person-years = 1.88 (1.76- 2.00)**		
Variables	**Total Cohort n(%)**	**HR (95% CI)***
Socio-demographic and socioeconomic factors		
Age		
Mean (SD)	57.4 (17.0)	**1.1 (1.06-1.07)**
Gender		
Female	427 (46.4)	Reference
Male	493 (53.6)	**1.4 (1.2-1.6)**
Ethnicity group		
British	468 (50.9)	Reference
Other White	91 (9.9)	0.8 (0.6- 1.0)
Asian	54 (5.9)	0.8 (0.6- 1.0)
Caribbean	140 (15.2)	**0.7 (0.6- 0.9)**
Black African	129 (14.0)	**0.8 (0.7- 0.9)**
Other	38 (4.1)	0.8 (0.6- 1.2)
Relationship status		
No relationship	808 (87.8)	Reference
Relationship	112 (12.2)	**0.8 (0.6- 0.9)**
Employment		
Not in paid employment	910 (98.9)	Reference
Paid employment	10 (1.1)	0.6 (0.3- 1.1)
Deprivation level in area of residence		
Low level	328 (35.7)	Reference
Medium level	299 (32.8)	1.0 (0.9- 1.2)
High level	283 (30.9)	0.9 (0.8- 1.1)
Homelessness	5 (0.6)	0.6 (0.2- 1.4)
Clinical factors		
Diagnosis		
Schizophrenia (ICD-10: F20)	690 (75.0)	Reference
Schizoaffective disorder (ICD-10: F25)	60 (6.5)	0.9 (0.7- 1.2)
Bipolar affective disorder (ICD-10: F31)	170 (18.5)	0.9 (0.8- 1.1)
Comorbid Depression		
No	816 (88.7)	Reference
Yes	104 (11.3)	0.9 (0.7- 1.2)

Comorbid Personality Disorder		
No	858 (93.3)	Reference
Yes	62 (6.7)	1.2 (0.9- 1.6)
Comorbid Substance Use		
No	835 (90.8)	Reference
Yes	85 (9.2)	**1.7 (1.3- 2.1)**
Time known to SLAM		
Mean (SD)	1667.15 (996.7)	1.0 (0.9999- 1.0000)
%BNF		
Mean (SD)	53.95 (49.7)	1.0 (0.9991- 1.0017)
Olanzapine equivalence dose		
1-10mg	373 (45.5)	Reference
11-20mg	211 (25.7)	0.9 (0.8- 1.2)
21+mg	236 (28.8)	1.1 (0.9- 1.3)
Smoking		
Never smoked	301 (32.7)	Reference
Have smoked ever	619 (67.3)	**1.5 (1.3- 1.8)**

***** All HR have been age and gender adjusted

8.4.1 Antipsychotic regimen and all-cause mortality

Table 8.3 summarises the sample characteristics by antipsychotic monotherapy and polypharmacy group. In total, 8,421 (76.9%) sample cases were prescribed long-term monotherapy, of whom 758 (9%) died in the follow-up. A further 2,524 sample cases (23%) were prescribed long-term antipsychotic polypharmacy, of whom 162 (6.4%) died. Patients prescribed monotherapy differed significantly from those prescribed polypharmacy across all socio-demographic, socioeconomic, clinical and smoking characteristics apart from comorbid substance use, where a comparable proportion of patients received a comorbid substance use diagnoses. Patients prescribed antipsychotic polypharmacy were on average younger, more likely to be of black African or Caribbean ethnicity, less likely to be in a relationship or employed and had a higher level of deprivation. Furthermore, antipsychotic polypharmacy patients were more likely to be diagnosed with schizophrenia, whereas patients on monotherapy had a higher prevalence of bipolar affective disorder diagnosis. However, patients on monotherapy were more likely to have a comorbid depression diagnosis, whereas patients on polypharmacy had a higher prevalence of personality disorders. Polypharmacy prescribed patients were known to mental health service for longer, were more likely to receive a high antipsychotic dose (as measured by both %BNF and olanzapine equivalence) and to have ever smoked.

Table 8.3 Sample characteristics of patients prescribed monotherapy and antipsychotic polypharmacy. (n=10,945)

Antipsychotic Monotherapy **Total person-time at risk (years) =39,474** **Rate per 100 person-years = 1.92 (1.79- 2.06)** **Antipsychotic Polypharmacy** **Total person-time at risk (years) =9,551** **Rate per 100 person-years = 1.70 (1.45- 1.98)**			
Variables	**Monotherapy** **n (%)**	**Antipsychotic polypharmacy** **n (%)**	**Test for significance**
Total	8,421 (76.9)	2,524(23.1)	
Deaths	758 (9.0)	162 (6.4)	$X^2(1)=16.83$, p<0.001
Socio-demographic and socioeconomic factors			
Age Mean (SD)	42.2 (15.4)	38.1 (13.5)	t(10943)=12.13, p<0.001
Gender			
Female	3,737 (44.4)	1,054 (41.8)	$X^2(1)=5.40$, p=0.02
Male	4,684 (55.6)	1,470 (58.2)	
Ethnicity group			
British	3,160 (37.6)	838 (33.2)	$X^2(5)=49.76$, p<0.001
Other White	791 (9.4)	184 (7.3)	
Asian	566 (6.7)	159 (6.3)	
Caribbean	1,072 (12.7)	354 (14.0)	
Black African	2,198 (26.1)	813 (32.2)	
Other	634 (7.5)	176 (7.0)	
Employment			
Not in paid employment	8,132 (96.6)	2,461 (97.5)	$X^2(1)=5.46$, p=0.02
Paid employment	289 (3.4)	63 (2.5)	
Relationship status			
No relationship	7,198 (85.5)	2,303 (91.2)	$X^2(1)=56.39$, p<0.001
Relationship	1,223 (14.5)	221 (8.8)	
Deprivation level in area of residence			
Low level	2,726 (32.6)	805 (32.2)	$X^2(3)=10.54$, p=0.01
Medium level	2,758 (33.0)	808 (32.3)	
High level	2,742 (32.8)	821 (32.9)	
Homelessness	135 (1.6)	65 (2.6)	

Clinical factors			
Schizophrenia (ICD-10: F20)	5,896 (70.0)	1,950 (77.3)	$X^2(2)=98.21$, p<0.001
Schizoaffective disorder (ICD-10: F25)	639 (7.6)	235 (9.3)	
Bipolar affective disorder (ICD-10: F31)	1,886 (22.4)	339 (13.4)	
Comorbid Depression			
No	7,235 (85.9)	2,223 (88.1)	$X^2(1)=7.71$, p=0.006
Yes	1,186 (14.1)	301 (11.9)	
Comorbid Personality Disorder			
No	7,642 (90.8)	2,145 (85.0)	$X^2(1)=68.22$, p<0.001
Yes	779 (9.2)	379 (15.0)	
Comorbid Substance Use			
No	7,581 (90.0)	2,252 (89.2)	$X^2(1)=1.37$, p=242
Yes	840 (10.0)	272 (10.8)	
Time known to SLAM			
Mean (SD)	1603.5 (1138.2)	2223.9 (1468.9)	t(10943)=-22.36, p<0.001
%BNF			
Mean (SD)	45.8 (36.8)	101.8 (68.8)	t(10020)=-50.84, p<0.001
Olanzapine equivalence dose			
1-10mg	4,341 (55.7)	134 (6.0)	$X^2(2)=3.1$, p<0.001
11-20mg	2,427 (31.2)	557 (25.0)	
21+mg	1,022 (13.1)	1,536 (69.0)	
Smoking			
Never smoked	3,016 (35.8)	374 (14.8)	$X^2(1)=400.46$, p<0.001
Have smoked ever	5,405 (64.2)	2,150 (85.2)	

Antipsychotic dose information was available for 92% of the sample. Therefore the total cohort sample for the analysis including %BNF dose was n=10,022. Gardner et al. (Gardner et al. 2010), do not provide an olanzapine equivalent dose for asenapine, therefore five further cases were dropped resulting in n=10,017 for the analysis including olanzapine equivalence dose.

Tables 8.4 and 8.5 summarise the prescribing patterns for specific antipsychotic groups (such as first and second generation antipsychotics) by antipsychotic regimen and %BNF dose (Table 8.4); and olanzapine equivalence dose (Table 8.5). Overall, following a chi-square test, there was a higher proportion of FGA prescribing for patients on a high-dose monotherapy regimen, as categorized by both %BNF and olanzapine equivalence.

Table 8.4 Distribution of antipsychotics by generation across low, medium and high %BNF doses for antipsychotic monotherapy and polypharmacy.

Regimen	Monotherapy				Antipsychotic polypharmacy			
Dose	**1-49%**	**50-100%**	**101%+**	**p-value**	**1-49%**	**50-100%**	**101%+**	**p-value**
FGA n (%)	920 (21.0)	414 (13.2)	184 (69.7)	$x^2(2)=511.46$, $p<0.001$	25 (7.1)	56 (5.7)	38 (4.2)	$X^2(2)=4.52$, $p=0.104$
SGA n (%)	3,460 (79.0)	2,735 (86.8)	80 (30.3)		331 (92.9)	918 (94.3)	861 (95.8)	

Table 8.5 Distribution of antipsychotic type by generation across low, medium and high olanzapine equivalence dose categories for monotherapy and polypharmacy.

Regimen	Monotherapy				Antipsychotic polypharmacy			
Dose	**1-10mg**	**11-20mg**	**21+mg**	**p-value**	**1-10mg**	**11-20mg**	**21+mg**	**p-value**
FGA n (%)	469 (10.8)	277 (11.4)	772 (75.5)	$X^2(2)=2.4$, p<0.001	1 (0.8)	9 (1.6)	109 (7.1)	$X^2(2)=30.23$, p<0.001
SGA n (%)	3,872 (89.2)	2,150 (88.6)	250 (24.5)		133 (99.2)	548 (98.4)	1,427 (92.9)	

Figure 8.2 represents the Kaplan–Meier curves comparing mortality over time for patients prescribed either long-term antipsychotic monotherapy or polypharmacy. There was no significant difference in mortality across the two groups over time (p= 0.1656).

Figure 8.2 Kaplan-Meier survival curves comparing mortality over time of patients prescribed either long-term antipsychotic monotherapy or polypharmacy. (n=10,945)

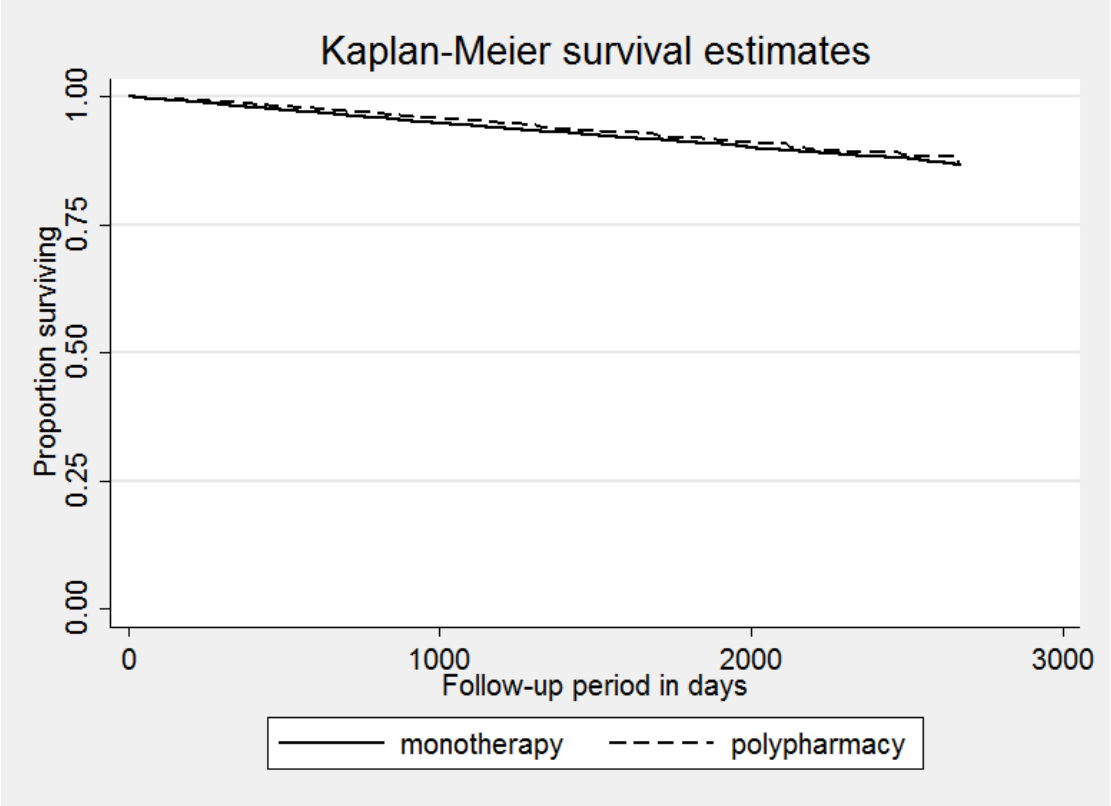


Table 8.6 summarises Cox proportional hazards models of the associations between being prescribed long-term antipsychotic polypharmacy and all-cause mortality. Age and gender appeared to have a negative confounding effect, and adjusting for those in the multivariable model, increased the strength of the association of interest. Adjusting the model for smoking resulted in a decrease in the strength of the association, and the association was no longer statistically significant. The fully adjusted model indicated a slightly elevated risk, but this was not statistically significant. Furthermore, the association remained unchanged after I adjusted for propensity scores, in place of the above factors. A likelihood ratio test revealed no interaction between either dose [%BNF (p=0.083); olanzapine equivalence (p=0.1510)] and antipsychotic regimen for all-cause mortality. I included %BNF and olanzapine equivalence dose as covariates in two separate models. The %BNF dose adjustment revealed a modest significant association between polypharmacy prescribing and death; however this association was not significant in the model where olanzapine equivalence was included as a covariate. I further conducted several sensitivity analyses, described in Table 8.7. Although restricting the analysis to patients not prescribed clozapine, or to patients prescribed FGAs, indicated no association between antipsychotic polypharmacy prescribing and risk of death, restricting the analysis to patients residing within the SLAM catchment, and to patients with a propensity score indicating they could have been prescribed both monotherapy and polypharmacy, indicated similar risk for all-cause mortality, which was just below statistical significance. Patients with a propensity score ranging from

0.023 to 0.631 were considered to be at risk for both antipsychotic monotherapy and polypharmacy.'

Table 8.6 Multivariable Cox regression analysis of the association between antipsychotic polypharmacy prescribing and mortality in individuals with serious mental illness.

N = 10,945 **Number of deaths = 920** **Total person-time at risk (years) =49,026** **Rate per 100 person-years = 1.88 (1.76- 2.00)**		
Association between antipsychotic polypharmacy and mortality **Models**	**Antipsychotic polypharmacy v monotherapy** **HR (95% CI)**	**p value**
Unadjusted Model	0.9 (0.7- 1.1)	p=0.166
Model adjusted for age and gender	**1.2 (1.0- 1.5)**	**p=0.016**
Model adjusted for socio-demographic[a] and socioeconomic[b] factors	**1.2 (1.0- 1.5)**	**p=0.020**
Model adjusted for age, gender and clinical factors [c]	**1.2 (1.0- 1.5)**	**p=0.017**
Model adjusted for age, gender and smoking	1.1 (0.9- 1.4)	p=0.111
Fully adjusted model	1.2 (0.9- 1.4)	p=0.079
Fully adjusted model by using propensity score as a covariate	1.2 (0.9- 1.4)	p=0.084
Fully adjusted model and %BNF dose	**1.3 (1.0- 1.5)**	**p=0.031**
Fully adjusted model and olanzapine equivalence dose	1.2 (0.9- 1.5)	p=0.088

[a] socio-demographic factors included age, gender, ethnicity, relationship status

[b] socioeconomic factors included employment and deprivation level

[c] clinical factors comprised comorbid depression, personality disorder and substance use; and time known to SLAM services.

Table 8.7 Sensitivity analyses of the association between antipsychotic polypharmacy prescribing and all-cause mortality in individuals with serious mental illness.

N = 10,945 **Number of deaths = 920** **Total person-time at risk (years) =49,026** **Rate per 100 person-years = 1.88 (1.76- 2.00)**		
Fully[a] adjusted models	**HR (95% CI)**	**p value**
Analysis restricted to patients not prescribed clozapine	1.1 (0.9- 1.4)	p=0.266
Analysis restricted to patients prescribed FGA	1.1 (0.9- 1.4)	p=0.444
Analysis restricted to patients residing within SLAM	1.2 (0.9- 1.4)	p=0.076
Analysis restricted to patients who were at risk of being prescribed both monotherapy and polypharmacy (based on propensity scores)	1.2 (0.9- 1.4)	p=0.085
Analysis restricted to patients with schizophrenia (ICD-10: F20)	1.2 (0.9- 1.5)	p=0.084
Analysis restricted to patients with ICD 10:F31 diagnosis	1.2 (0.7- 2.1)	p=0.609

[a] age, gender, ethnicity, relationship status, employment, deprivation level, comorbid depression, personality disorder and substance use, time known to SLAM services and smoking.

8.4.2 Antipsychotic dose and all-cause mortality

Table 8.8 and 8.9 summarise the cohort composition by %BNF dose and olanzapine equivalence dose, respectively. There were significant differences in characteristics across categories, for both %BNF and olanzapine equivalence dose. Overall, patients prescribed lower dose (for both %BNF and olanzapine equivalence dose) were more likely to be of British ethnicity, to be in a relationship, to be employed, to have a bipolar affective disorder diagnosis, and comorbid depression diagnosis. Patients prescribed a high antipsychotic dose were more likely to live in a more deprived area (based on deprivation index score), to have a schizophrenia diagnosis, comorbid personality disorder diagnosis, to have smoked and to have been known to SLAM services for longer.

Table 8.8 Sample characteristics by percentage out of the maximum BNF recommended dose for antipsychotic medications.

N = 10,945 **Low dose** **Total person-time at risk (years) =21,299** **Rate per 100 person-years = 2.00 (1.81- 2.19)** **Medium dose** **Total person-time at risk (years) =18,376** **Rate per 100 person-years = 1.64 (1.46- 1.84)** **High dose** **Total person-time at risk (years) =4,677** **Rate per 100 person-years = 1.96 (1.60- 2.40)**				
Dose Category n(%)	**Low dose (1-49%)** 4,736 (47.3) **n(%)**	**Medium dose (50-100%)** 4,123 (41.1) **n(%)**	**High dose (101% +)** 1,163 (11.6) **n(%)**	**Test for significance**
Total Death	426 (52.0)	302 (36.8)	92 (11.2)	$X^2(2)=8.31$, p=0.016
Age				
Mean (SD)	42.9 (16.1)	39.5 (13.9)	39.9 (14.5)	F(2,10019)=58.06, p<0.001
Gender				
Male	2,395 (50.6)	2,511 (60.9)	701 (60.3)	$X^2(2)=105.47$, p<0.001
Ethnicity group				
British	1,872 (39.5)	1,405 (34.1)	415 (35.7)	$X^2(10)=63.82$, p<0.001
Other White	438 (9.2)	384 (9.3)	74 (6.4)	
Asian	335 (7.2)	261 (6.3)	82 (7.0)	
Caribbean	569 (12.0)	515 (12.5)	175 (15.0)	
Black African	1,165 (24.6)	1,230 (29.8)	342 (29.4)	
Other	357 (7.5)	328 (8.0)	75 (6.5)	
Relationship status				
Relationship	760 (16.1)	489 (11.9)	105 (9.0)	$X^2(2)=55.68$, p<0.001
Employment				
Paid employment	184 (3.9)	109 (2.6)	27 (2.3)	$X^2(2)=14.22$, p<0.001
Deprivation level in area of residence				
Low level	1,639 (34.8)	1,263 (30.9)	357 (31.1)	$X^2(6)=30.24$, p<0.001
Medium level	1,528 (32.5)	1,372 (33.6)	370 (32.2)	
High level	1,472 (31.3)	1,364 (33.4)	388 (33.8)	
Homelessness	65 (1.4)	89 (2.2)	33 (2.9)	
Diagnosis				
ICD-10: F20	3,241 (68.4)	3,008 (73.0)	903 (77.6)	$X^2(4)=122.56$, p<0.001
ICD-10: F25	320 (6.8)	356 (8.6)	119 (10.2)	
ICD-10: F31	1,175 (24.8)	759 (18.4)	141 (12.1)	
Comorbid Depression				

Yes	745 (15.7)	516 (12.5)	117 (10.1)	$X^2(2)=34.32$, $p<0.001$
Comorbid Personality Disorder				
Yes	450 (9.5)	435 (10.6)	167 (14.4)	$X^2(2)=23.47$, $p<0.001$
Comorbid Substance Use				
Yes	385 (8.1)	511 (12.4)	123 (10.6)	$X^2(2)=44.13$, $p<0.001$
Time known to SLAM				
Mean (SD)	1601.6 (1089.6)	1763.6 (1404.5)	2186.0 (1241.4)	$F(2,10019)=100.37$, $p<0.001$
Smoking				
Have smoked ever	2,880 (60.8)	3,040 (73.7)	967 (83.2)	$X^2(2)=298.63$, $p<0.001$

Table 8.9 Sample characteristics by olanzapine equivalence dose group.

N = 10,945
Low dose
Total person-time at risk (years) =19,512
Rate per 100 person-years = 1.91 (1.73- 2.11)

Medium dose
Total person-time at risk (years) =13,525
Rate per 100 person-years = 1.56 (1.36- 1.79)

High dose
Total person-time at risk (years) =11,310
Rate per 100 person-years = 2.09 (1.83- 2.37)

Olanzapine equivalence category n(%)	**Low dose 1-10mg** 4,475 (44.7) **n(%)**	**Medium dose 11-20mg** 2,984 (29.8) **n(%)**	**High dose 21mg +** 2,558 (25.5) **n(%)**	**Test for significance**
Total Death	373 (45.5)	211 (25.7)	236 (28.8)	$X^2(2)=8.75$, p=0.01
Age				
Mean (SD)	41.67 (16.3)	39.82 (14.0)	41.85 (14.2)	F(2,10014)=16.96, p<0.001
Gender				
Male	2,179 (48.7)	1,835 (61.5)	1,589 (62.1)	$X^2(2)=172.33$, p<0.001
Ethnicity group				
British	1,721 (38.5)	1,039 (34.8)	931 (36.4)	$X^2(10)=89.40$, p<0.001
Other White	441 (9.9)	281 (9.4)	173 (6.8)	
Asian	314 (7.0)	210 (7.0)	154 (6.0)	
Caribbean	495 (11.1)	341 (11.4)	423 (16.5)	
Black African	1,141 (25.4)	881 (29.6)	715 (27.9)	
Other	363 (8.1)	232 (7.8)	162 (6.4)	
Relationship status				
Relationship	765 (17.1)	359 (12.0)	229 (8.9)	$X^2(2)=100.30$, p<0.001
Employment				
Paid employment	199 (4.5)	71 (2.4)	50 (1.9)	$X^2(2)=41.82$, p<0.001
Deprivation level in area of residence				
Low level	1,524 (34.3)	930 (31.5)	804 (31.7)	$X^2(6)=22.51$, p=0.001
Medium level	1,462 (32.9)	1,003 (34.0)	805 (31.8)	
High level	1,390 (31.2)	972 (32.9)	858 (33.9)	
Homelessness	73 (1.6)	46 (1.6)	68 (2.7)	
Diagnosis				
ICD-10: F20	2,844 (63.5)	2,228 (74.7)	2,079 (81.3)	$X^2(4)=408.41$, p<0.001
ICD-10: F25	321 (7.2)	247 (8.3)	227 (8.9)	
ICD-10: F31	1,310 (29.3)	509 (17.1)	252 (9.9)	

Comorbid Depression				
Yes	809 (18.1)	357 (11.9)	211 (8.3)	$X^2(2)=144.03$, $p<0.001$
Comorbid Personality Disorder				
Yes	431 (9.6)	316 (10.6)	305 (11.9)	$X^2(2)=9.13$, $p=0.01$
Comorbid Substance Use				
Yes	391 (8.7)	355 (11.9)	273 (10.7)	$X^2(2)=20.49$, $p<0.001$
Time known to SLAM				
Mean (SD)	1511.3 (1094.1)	1732.7 (1476.6)	2133.5 (1148.9)	$F(2,10014)=232.85$, $p<0.001$
Smoking				
Have smoked ever	2,671 (59.7)	2,177 (72.9)	2,036 (79.6)	$X^2(2)=335.48$, $p<0.001$

Table 8.10 summarises the crude and fully adjusted Cox regression analyses between antipsychotic dose and the risk for all-cause mortality. I found no evidence to indicate that dose had an effect on the risk of death for patients with SMI. The results were very similar for both percentage BNF and olanzapine equivalence dose.

Table 8.10 Multivariable Cox analysis of the association between all cause mortality and antipsychotic dose.

Dose calculated as %BNF[a]	HR (95% CI)	p-value
Unadjusted Model	1.0 (0.997- 1.000)	p= 0.064
Fully[b] Adjusted Model	1.0 (0.999- 1.001)	p= 0.996
Dose calculated as olanzapine equivalence[c]		
11- 20mg		
Unadjusted Model	**0.8 (0.7- 0.9)**	**p= 0.018**
Fully[b] Adjusted Model	0.9 (0.8- 1.1)	p= 0.532
21+ mg		
Unadjusted Model	1.1 (0.9- 1.3)	p= 0.296
Fully[b] Adjusted Model	1.1 (0.9- 1.3)	p= 0.377

[a] %BNF used as continuous variable

[b] Factors included: age, gender, ethnicity, relationship status, employment, deprivation level, comorbid depression, personality disorder, substance use, time known to SLAM services and smoking.

[c] low dose (1-10mg) was used as the reference group for the analysis.

8.4.3 Antipsychotic regimen and cause-specific mortality

Cause of death was available for 892 (97%) of all deaths recorded for the monotherapy and polypharmacy groups. Table 8.11 summarises the prevalence of natural and unnatural causes of deaths across the two antipsychotic regimens.

As illustrated by Table 8.12, patients who died from unnatural causes of death were younger, more likely to be of black African, Asian or Other ethnicity, in comparison to patients dying from natural causes of death. Furthermore, this group had significantly more comorbid personality disorder, substance use, and overall higher percentage BNF antipsychotic dose.

Table 8.11 Causes of death by antipsychotic monotherapy and polypharmacy medication group. (n=892 deaths)

N = 10,945 **Natural Deaths= 783** **Total person-time at risk (years) =49,025** **Rate per 1000 person-years = 15.97 (14.89- 17.13)** **Unnatural deaths= 109** **Total person-time at risk (years) =49,025** **Rate per 1000 person-years = 2.22 (1.84- 2.68)**			
Cause of death	**n**	**Monotherapy n(%)**	**Antipsychotic polypharmacy n(%)**
Natural		**652**	**131**
Infections	10	8 (1.1)	2 (1.3)
Neoplasms	153	131 (17.8)	22 (14.3)
Immune	7	5 (0.7)	2 (1.3)
Endocrine	33	26 (3.5)	7 (4.5)
Mental	68	52 (7.1)	16 (10.3)
Nervous system	25	22 (2.9)	3 (1.9)
Circulatory	211	175 (23.7)	36 (23.2)
Respiratory	159	131 (17.8)	28 (18.1)
Digestive	57	50 (6.8)	7 (4.5)
Skin and Muscle	10	10 (1.4)	0
Genitourinary	19	16 (2.2)	3 (1.9)
Not elsewhere	31	26 (3.5)	5 (3.2)
Unnatural		**85**	**24**
External causes	109	85 (11.5)	24 (15.5)

Table 8.12 Sample characteristics by natural and unnatural causes of death. (n=892)

Variables	Natural (n783) n(%)	Unnatural (n109) n(%)	Test for significance
Socio-demographic and socioeconomic factors			
Age			
Mean (SD) min-max	60.6 (15.3)	40.7 (16.1)	**t(890)=12.65, p<0.001**
Gender			
Female	381 (48.7)	40 (36.7)	**X^2(1)=5.49, p=0.019**
Male	402 (51.3)	69 (63.3)	
Ethnicity group			
British	414 (52.9)	53 (48.6)	**X^2(5)=17.42, p=0.004**
Other White	84 (10.7)	5 (4.6)	
Asian	41 (5.2)	9 (8.3)	
Caribbean	120 (15.3)	13 (11.9)	
Black African	97 (12.4)	18 (16.5)	
Other	27 (3.4)	11 (10.1)	
Relationship status			
No relationship	685 (87.5)	100 (91.7)	X^2(1)=1.64, p=0.200
Relationship	98 (12.5)	9 (8.3)	
Employment			
Not in paid employment	776 (99.1)	108 (99.1)	X^2(1)=0.0006, p=0.981
Paid employment	7 (0.9)	1 (0.9)	
Deprivation level in area of residence			
Low level	290 (37.2)	40 (36.7)	X^2(3)=4.58, p=0.206
Medium level	244 (31.3)	38 (34.9)	
High level	242 (31.1)	29 (26.6)	
Homelessness	3 (0.3)	2 (1.8)	
Clinical factors			
Diagnosis			
ICD-10: F20	588 (75.1)	75 (68.8)	X^2(2)=2.23, p=0.327
ICD-10: F25	50 (6.4)	10 (9.2)	
ICD-10: F31	145 (18.5)	24 (22.0)	
Comorbid Depression			
No	696 (88.9)	95 (87.2)	X^2(1)=0.28, p=0.593
Yes	87 (11.1)	14 (12.8)	
Comorbid Personality Disorder			
No	740 (94.5)	92 (84.4)	**X^2(1)=15.57, p<0.001**
Yes	43 (5.5)	17 (15.6)	

Comorbid Substance Use			
No	721 (92.1)	90 (82.6)	**$X^2(1)=10.48$, p=0.001**
Yes	62 (7.9)	19 (17.4)	
Time known to SLAM			
Mean (SD)	1686 (1016.8)	1598 (967.0)	t(890)=0.86, p=0.720
%BNF dose			
Mean (SD)	51.6 (49.5)	64.9 (49.8)	**t(796)=-2.54, p<0.001**
Olanzapine equivalence dose			
1-10mg	318 (45.7)	49 (48.0)	$X^2(2)=0.60$, p=0.739
11-20mg	182 (26.1)	23 (22.6)	
21mg+	196 (28.2)	30 (29.4)	
Smoking			
Never smoked	266 (34.0)	33 (30.3)	$X^2(1)=0.58$, p=0.444
Have smoked ever	517 (66.0)	76 (69.7)	

Table 8.13 summarises the competing risk regression analysis of the associations between being prescribed long-term antipsychotic polypharmacy and natural causes of death. Age and gender appeared to have a negative confounding effect, and adjusting for those in the multivariable model, resulted in an increase in the strength of the association with natural causes of death. However, adjusting for smoking reduced the strength of the association, below the statistical significance level. Similarly, the fully adjusted model indicated a modest effect of antipsychotic polypharmacy on natural causes of death, which did not reach statistical significance.

A likelihood ratio test revealed a significant interaction between dose [for both %BNF (p=0.046) and olanzapine equivalence dose (p=0.029)] and antipsychotic polypharmacy for natural causes of death. A crude stratification of antipsychotic polypharmacy by dose indicated that antipsychotic polypharmacy of high dose (for both %BNF and olanzapine equivalence) were associated with a lower risk for natural causes of death. However, this association was not maintained in the fully adjusted models for both %BNF and olanzapine equivalence (Table 8.14).

Table 8.13 Competing risk regression analysis of the association between antipsychotic polypharmacy prescribing and natural causes of death in individuals with serious mental illnesses. (n=783 natural deaths; n=10,945 total sample)

Association between antipsychotic polypharmacy and natural causes of death	**Antipsychotic polypharmacy v monotherapy**	
Models	**HR (95% CI)**	**p-value**
Unadjusted Model	0.8 (0.7- 1.0)	p= 0.062
Model adjusted for age and gender	**1.3 (1.0- 1.5)**	**p= 0.016**
Model adjusted for socio-demographic[a] and socioeconomic[b] factors	**1.3 (1.0- 1.5)**	**p= 0.020**
Model adjusted for age, gender and clinical factors[c]	**1.3 (1.0- 1.5)**	**p= 0.024**
Model adjusted for age, gender and smoking	1.2 (0.9- 1.4)	p= 0.102
Fully adjusted model	1.2 (0.9- 1.4)	p= 0.111

[a] socio-demographic factors included age, gender, ethnicity, relationship status
[b] socioeconomic factors included employment and deprivation level
[c] clinical factors included comorbid depression, personality disorder and substance use; time known to SLAM services.

Table 8.14 Competing risk regression analysis of the association between antipsychotic polypharmacy prescribing and natural causes of death, stratified by %BNF dose and olanzapine equivalence dose.

%BNF dose	**1-49%** **HR (95% CI)**	**50-100%** **HR (95% CI)**	**101%+** **HR (95% CI)**
Crude model	1.1 (0.8- 1.7)	0.9 (0.7- 1.3)	**0.6 (0.4- 0.9)**
Fully[a] adjusted model	1.5 (0.9- 2.4)	1.1 (0.8- 1.5)	1.4 (0.8- 2.3)
Olanzapine equivalence dose	**1-10mg** **HR (95% CI)**	**11-20mg** **HR (95% CI)**	**21+mg** **HR (95% CI)**
Crude model	1.1 (0.5- 2.2)	1.1 (0.7- 1.7)	**0.6 (0.4- 0.8)**
Fully[a] adjusted model	1.9 (0.9-3.9)	1.4 (0.9- 2.1)	1.1 (0.8- 1.4)

[a] age, gender, ethnicity, relationship status, employment, deprivation level, comorbid depression, personality disorder and substance use, time known to SLAM services, and smoking.

Table 8.15 summarises the competing risk regression analysis for unnatural causes of death and long-term antipsychotic polypharmacy. I found no evidence to suggest that long-term antipsychotic polypharmacy prescribing was associated with a change in risk for unnatural causes of death. As indicated by a likelihood ratio test, there was no interaction between polypharmacy and dose with unnatural causes of death as the outcome [%BNF (p=0.1903); olanzapine equivalence dose (p=0.1556)]. I included %BNF and olanzapine equivalence dose, sequentially in the fully adjusted model to examine if dose had an effect on the overall association. Dose had little effect on the overall association.

Table 8.15 Competing risk regression analysis of the association between antipsychotic polypharmacy prescribing and unnatural causes of death in individuals with serious mental illness. (n=109 unnatural deaths; n=10,945 total sample)

Association between antipsychotic polypharmacy and unnatural causes of death	Antipsychotic polypharmacy v Monotherapy	
Models	**HR (95% CI)**	**p value**
Unadjusted Model	1.1 (0.7- 1.8)	p= 0.601
Model adjusted for age and gender	1.1 (0.7- 1.8)	p= 0.669
Model adjusted for socio-demographic[a] and socioeconomic[b] factors	1.1 (0.7- 1.8)	p= 0.677
Model adjusted for age, gender and clinical factors[c]	1.1 (0.7- 1.8)	p= 0.654
Model adjusted for age, gender and smoking	1.1 (0.7- 1.8)	p= 0.698
Fully adjusted model	1.1 (0.7- 1.9)	p= 0.619
Fully adjusted model and %BNF	0.9 (0.6- 1.7)	p= 0.960
Fully adjusted model and Olanzapine equivalence dose	1.1 (0.6- 1.9)	p= 0.821

[a] socio-demographic factors included age, gender, ethnicity, relationship status
[b] socioeconomic factors included employment and deprivation level
[c] clinical factors included comorbid depression, personality disorder, substance use and time known to SLAM services.

8.4.4 Additional analysis

In order to investigate whether patients with a first episode of monotherapy was the most appropriate reference group, I extracted information and conducted analyses using two additional reference groups, where first episode of long-term polypharmacy was compared to: 1) a long-term monotherapy episode that occurred at or after the midpoint of the observation window (2010) (Appendix C); 2) everyone else in the sample who did not qualify for the long-term antipsychotic polypharmacy group (Appendix D). The latter group included patients who were on long-term monotherapy and all other patients who were known to SLAM services for six or more months and that did not qualify for the polypharmacy group. Changing the reference group made little difference to the overall findings in the fully adjusted Cox regression models, suggesting that the use of the first episode of long-term monotherapy, as the primary reference group was reasonable. The last monotherapy episode was not considered as an alternative reference group as it is likely to have occurred too close to the end of the observation period, thus limiting follow-up time.

In addition I also conducted an analysis comparing the risk of all-cause mortality between patients prescribed clozapine as a monotherapy as opposed to polypharmacy. In total 540 (51.63) patients were prescribed clozapine monotherapy and 506 (48.37) were prescribed clozapine polypharmacy. A fully adjusted Cox analysis indicated no statistically significant difference in the risk of death between the two groups: HR 1.3 (95% CI: 0.9- 2.2), p=0.184. It is possible that there was not a sufficient power to detect an effect, in total there were 78 deaths between the two groups.

8.5 Discussion

As far as I am aware, this is the first study to investigate the association between regular long-term antipsychotic polypharmacy use and all-cause and cause-specific mortality in a large and diverse cohort, adjusting for multiple confounders, in addition to investigating the effects of combined antipsychotic dose. I hypothesised that long-term antipsychotic polypharmacy would be associated with an increased risk for all-cause mortality and, specifically, of death from natural causes. The results indicated a weak association between long-term antipsychotic use with all-cause mortality and with natural causes of death, after adjusting for gender and age. Although these associations were not markedly confounded by other factors, the fully adjusted hazard ratios fell below statistical significance in most models. The association with unnatural causes of death was weaker still, and no evidence was found that factors such as antipsychotic dose had a direct effect on the risk of death in this sample with SMI or confounded the associations between antipsychotic polypharmacy and mortality.

8.5.1 Antipsychotic polypharmacy and all-cause mortality

In keeping with existing literature, I found that patients prescribed antipsychotic polypharmacy were younger, less likely to be employed, less likely to be in a relationship, had a higher proportion of schizophrenia diagnosis and were known to services for longer, in comparison to patients on monotherapy (Correll & Gallego 2012; Ganguly et al. 2004; Kreyenbuhl et al. 2007; Morrato et al. 2007). However, aside from gender and age, the

aforementioned factors seemed to have only a small effect on the strength of the association between long-term antipsychotic polypharmacy and all-cause mortality.

Overall, the literature to date examining antipsychotic polypharmacy and the risk of death in SMI has been mixed and inconclusive (see Chapter 2 section 2.4.3). As I have previously described, there is some evidence from research including antipsychotic polypharmacy of unspecified duration, indicating that polypharmacy increases the risk for death (Waddington et al. 1998; Joukama et al. 2006). However, findings from larger epidemiological studies have been mixed, with evidence to indicate no association (Tiihonen et al. 2006; Baandrup et al. 2010) and possibly lower risk for mortality (Katona et al. 2014) in patients prescribed antipsychotic polypharmacy compared to those on monotherapy. My findings further indicate that the risk in the SMI cohort I examined is not clear-cut. There did appear to be a small effect of long-term antipsychotic polypharmacy on all-cause mortality and the strength of this association was similar in most models; however, the statistical significance of the association varied and was generally borderline (Table 8.6).

Evidence regarding the role of specific antipsychotics in the risk for death has been mixed (Kiviniemi et al. 2013; Hayes et al. 2014; Montout et al. 2002; Tenback et al. 2012; Tiihonen et al. 2009). There is some evidence to suggest that FGAs are associated with increased risk for mortality, whereas clozapine is associated with a decreased risk for death (Kiviniemi et al. 2013; Hayes et al. 2014; Montout et al. 2002; Tenback et al. 2012). In this study, the

prescribing of FGAs or clozapine, as part of the antipsychotic regimen, made no difference to the overall risk (see Table 8.7).

8.5.2 Antipsychotic polypharmacy and cause-specific mortality

People with schizophrenia have an increased risk for premature death from natural causes such as cardiovascular diseases (Kiviniemi et al. 2013; Osborn et al. 2014; Laursen et al. 2014; Joukama et al. 2001) and unnatural causes such as suicide (Osby et al. 2000; Reininghaus et al. 2015) compared to the general population. However, research examining the effect of long-term antipsychotic polypharmacy prescribing on cause-specific mortality has been extremely sparse. I was able to identify only one study, which examined the risk for cause-specific mortality in patients prescribed long-term polypharmacy. In this, Baandurp and colleagues (Baandrup et al. 2010) reported that the risk for natural causes of death did not increase when patients were prescribed two or more antipsychotics, as compared to monotherapy. Although my findings did not indicate a statistically significant difference between patients prescribed antipsychotic polypharmacy and monotherapy in most of the fully adjusted models, the association of polypharmacy with increased risk for natural causes of death changed little, once adjusted for gender and age, which might be indicative of a modest effect. Associations between long-term antipsychotic polypharmacy and unnatural cause of death were weaker and also not statistically significant.

8.5.3 Antipsychotic dose and mortality

In keeping with existing literature (Gisev et al. 2014; Grech & Taylor 2012; Roh et al. 2015), patients prescribed long-term antipsychotic polypharmacy were more likely to be prescribed a higher combined dose of antipsychotics in comparison to patients on long-term monotherapy; however adjusting for dose had very little effect on the association between antipsychotic polypharmacy and mortality. Also dose was not associated with mortality in the fully adjusted models. Previous research has indicated that high antipsychotic dose is associated with increased risk for all-cause mortality, and more specifically for cancer, cardiovascular and respiratory causes of death (Torniainen et al. 2015; Ray et al. 2009; Osborn et al. 2014). There are several possible factors that could offer an explanation for these differences in results across studies. It is possible that different methods of calculating antipsychotic dose would yield different results. Methods such as %BNF dose and defined daily dose (DDD) are calculated by using the upper licensed dose range of antipsychotics (Patel et al. 2013). This poses a problem for antipsychotics that reach their maximum efficacy at a lower dose range, such as risperidone, and which are thus rarely prescribed at maximum or above maximum recommended dose. Furthermore, over the years, there have been changes to the recommended maximum doses for some antipsychotics, which makes it difficult to compare findings from different studies across time. An alternative explanation for differences in findings across studies is the possibility of residual confounding. For example, although Torniainen et al. (Torniainen et al. 2015) used age and gender matched case and controls, their Cox model did not account for any other factors that may affect mortality such as

smoking, which is associated with significant risk for death (Goff et al. 2005; Brown et al. 2000).

There is some previous research (Langan & Shajahan 2010) that has suggested that the increased mortality observed in patients with SMI, could be a consequence of antipsychotic dose, rather than the antipsychotic regimen that is prescribed. Furthermore, a more recent study (Torniainen et al. 2015) found that the patients who were either receiving no antipsychotic treatment or very high dose antipsychotic treatment, had the highest mortality risk. In my study, I found no evidence to indicate that dose had an independent association with death.

8.5.4 Strengths

This study had several strengths. SLAM is close to being a monopoly mental health care provider for its geographic catchment (Stewart et al. 2009; Perera et al. 2016). Therefore, I was able to capture a large cohort of patients with SMI giving me the statistical power to adjust for a number of well-known and other potential confounders, such as smoking and antipsychotic dose, that other research has been unable to examine.

At present, there is no 'gold standard' for calculating equivalent doses (Patel et al. 2013); therefore I chose to use two different methods of calculating dose. Percentage out of the maximum BNF recommended dose has been recommended by the Royal College of Psychiatrists (Royal College of

Psychiatrists 2014) as one method of choice for calculating high dose prescribing in polypharmacy. Olanzapine equivalence dose method has gained popularity in recent years (Gardner et al. 2010; Gisev et al. 2014; Patel et al. 2013) in this field and is currently preferred to chlorpromazine equivalence. Furthermore, using two different approaches allowed me to test the effect of dose more rigorously and also demonstrate that existing evidence in this field needs to be interpreted with caution, as findings are dependent on the method that is used.

8.5.5 Limitations

There were several potential limitations in this study. Given the marginally significant results in relation to long-term antipsychotic polypharmacy prescribing with all-cause; and natural-causes of death, it is possible that I did not have sufficient statistical power to detect a consistently significant effect. However, the width of the confidence intervals did not suggest that there were particularly strong effects that were missed.

Furthermore, despite adjusting for multiple confounders, it is possible that some residual confounding may have occurred. I employed propensity scores as both a covariate and in a sensitivity analysis, where I restricted the analysis to patients at risk of being prescribed monotherapy and polypharmacy. Although this limited the chance for confounding by indication, it cannot be completely ruled out. In relation to confounders, the role of smoking as a covariate does need to be considered with some caution. Firstly, I did not

have data on the frequency of smoking to include in the models (only smoking status), so there may have been residual confounding as a consequence. Furthermore, adjustment for smoking presupposes a situation where people who go on to receive polypharmacy have more unhealthy lifestyles, including smoking, which account for any raised mortality in this group. However, it is possible that an effect of polypharmacy may be to maintain smoking behaviour, if this is used to counteract perceived or actual adverse effects of medication (Goff et al. 1992). Inclusion of smoking status as a covariate in this circumstance would represent an over-adjustment as it could be on the causal pathway between antipsychotic polypharmacy and mortality. Unfortunately it was not possible to tease out the timing of polypharmacy in relation to smoking status, and therefore these different pathways have yet to be distinguished.

Despite the potentially specific effects that certain antipsychotics, such as clozapine or groups of antipsychotics such as FGA, could have had on the overall association, examining specific combinations of antipsychotics was beyond the scope of the study. However, it is possible that the risk of death differs across certain combinations of antipsychotics (Kiviniemi et al. 2013; Hayes et al. 2014; Montout et al. 2002; Tenback et al. 2012).

I chose to compare polypharmacy with monotherapy treatment with a minimum duration of six months, as the reference group, therefore ensuring that all patients that qualified for the study were known to services for a minimum of six months. However, it is still possible that some survival bias

may have occurred in selecting the patients with a first episode of polypharmacy, as patients needed to have survived long enough to go from monotherapy to long-term antipsychotic polypharmacy. Furthermore it is possible that as a result of selecting patients who have had either antipsychotic regimen for six or more months, I was unable to detect acute outcomes that occurred within the six months prior to the patient entering the cohort. This could have possibly resulted in immortal time bias, as the patients had to survive long enough in order to enter either of the exposure groups. An additional limitation was that I was unable to determine the antipsychotic regimen at the time of death. Therefore, I was unable to determine how long patients were prescribed the antipsychotic regimens prior to their death.

8.5.6 Possible mechanisms

In seeking alternative mechanisms that could explain the mortality gap between patients with SMI and the general population, it is possible that polypharmacy regimen has an indirect effect on mortality. For example, there is some existing research that indicates that antipsychotic polypharmacy increases the risk for adverse drug reactions such as QTc prolongation, parkinsonian symptoms, hyperprolactinemia, dyslipidaemia and other metabolic problems such as weight gain and diabetes (Barbui et al. 2016; Gallego et al. 2012). Furthermore, antipsychotic polypharmacy has been associated with pre-metabolic syndrome (the presence of visceral fat obesity in addition to either elevated blood glucose or lipid abnormalities or elevated blood pressure), after adjusting for a number of confounders, indicating that

polypharmacy may act as a mediator on the causal pathway to mortality in individuals with SMI (Misawa et al. 2011). Further evidence also suggests that dose can also mediate this relationship (Barbui et al. 2016; Centorrino et al. 2004). Therefore, it is possible that the increased risk for death in people with SMI is a by-product of a complex interplay between different treatment factors and their side effects (not to mention consequences of side effects on lifestyle choices such as smoking behaviour, as previously mentioned). However, research investigating this remains too sparse to draw firm conclusions. Future research should aim to investigate causal pathways to mortality, including adverse drug reactions to general antipsychotic medications use and more specifically to polypharmacy.

8.5.7 Conclusion and implications

To date, despite the widespread practice of regimens such as antipsychotic polypharmacy, little is known about the long-term effects of its prescribing. Findings to date have been mixed and limited by methodological problems such as measuring antipsychotic polypharmacy of short duration, investigating small and homogeneous samples and difficulties with excluding residual confounding. The study described here is one of the first mortality studies to look specifically at the effects of long-term polypharmacy prescribing in a large clinical cohort that is representative of the population seen by secondary mental health care services, and considering a broad range of potential confounders. My findings suggest that the effect of long-term antipsychotic polypharmacy on mortality is not a clear-cut one. The effect of this regimen on

all-cause and natural causes of death was small and did not reach significance in most models. This has potential implications for further research. It is possible that if there is any effect on mortality, this is driven by specific antipsychotic medication combinations. Therefore, perhaps future research could focus on examining common antipsychotic combinations and their effect on particular cause of death, such as for example cardiovascular death, which from previous research, we know is particularly elevated in SMI population (Raedler 2010).

It is imperative to consider my findings and their implications within the wider context of antipsychotic polypharmacy treatment. Although I found that long-term antipsychotic polypharmacy does not increase the risk for death, in prescribing this regimen, it is important to bear in mind that polypharmacy continues to be associated with more severe side effects (Barbui et al. 2016; Gallego et al. 2012; Correll et al. 2007; Langan & Shajahan 2010). Furthermore, the notion that more is better, in relation to adding additional antipsychotics and increasing treatment dose, has been consistently rejected by empirical research (Lochmann van Bennekom et al. 2013; Taylor 2010), indicating that once an optimal dose and response is reached, adding additional treatments makes little difference. In certain circumstances increasing dose and/or adding an additional antipsychotic can be associated with lowering certain side effects (Taylor 2010; Joo-Cheol et al. 2007); however this needs to be done with caution. Lastly, evidence remains that polypharmacy is often prescribed in favour to clozapine monotherapy, despite research indicating that clozapine is effective in treating treatment- resistant

symptoms (Taylor et al. 2011). Although I was not able to assess reasons for not initiating clozapine prior to antipsychotic polypharmacy prescribing, previous research suggests that premature antipsychotic polypharmacy prescribing is likely to reflect a prescribing culture rather than evidence-based treatment (Howes et al. 2012). Therefore, the need to target this on prescriber and service level remains (Mace & Taylor 2015; Paton et al. 2008).

CHAPTER 9: DISCUSSION

9.1 Aim

The aim of this chapter is to discuss the findings of this thesis within the context of previous research but also in consideration of the wider patient, clinical, and treatment context. Furthermore, I also examine possible implications and directions for further research.

9.2 Summary of findings

The aims of the thesis were to:

1) To identify cases on long-term antipsychotic polypharmacy (≥ 6 months) prescribing in South London and Maudsley electronic health records (EHR).

2) To identify factors that predict long-term antipsychotic polypharmacy prescribing for SMI patients in secondary mental health care.

3) To investigate whether outcomes such as hospital readmission and mortality are associated with long-term antipsychotic polypharmacy prescribing in secondary mental health care.

Overall, this thesis provides evidence that EHRs can be successfully used to derive information on long-term antipsychotic polypharmacy prescribing in secondary mental health care with high precision (Chapter 5). Using SLAM de-identified health records (CRIS), I identified that being younger, residing in an area with a greater socioeconomic deprivation, having significant problems with clinical symptoms (positive psychotic symptoms), and greater previous

service use (prior outpatient contact, prior use of clozapine and/or long-acting injectables) were significant, independent predictors of long-term antipsychotic polypharmacy initiation (Chapter 6). Furthermore, patients prescribed antipsychotic polypharmacy at discharge were at increased risk for clinical outcomes such as hospital readmission into secondary mental health care (Chapter 7). Lastly, I found insufficient evidence to indicate that antipsychotic polypharmacy prescribing increases the risk for all-cause and cause-specific mortality. In addition, antipsychotic dose appeared to have little effect on mortality risk (Chapter 8).

9.3 How has this thesis advanced knowledge in this field?

9.3.1 Detecting antipsychotic polypharmacy prescribing using electronic health records

Existing literature examining antipsychotic polypharmacy has predominantly derived information from medical insurance databases (Boaz et al. 2013; Clark et al. 2002; Ganguly et al. 2004; Katona et al. 2014; Morrato et al. 2007; Ortiz et al. 2016). Although this has enabled researchers to examine large population samples, these datasets often do not contain detailed contextual information, such as that on patient symptoms and response to treatment, which is also regularly updated. Therefore, studies have examined fewer confounders, such as antipsychotic dose, leading to possible residual confounding (Suokas et al. 2012; Ortiz et al. 2016; Ganguly et al. 2004; Gallego et al. 2012; Faries et al. 2005; Clark et al. 2002; Katona et al. 2014; Tiihonen et al. 2012). Conversely, studies that have used text-rich databases

such as clinical records (Barbui et al. 2006; Moilanen et al. 2016; Centorrino et al. 2004) have examined smaller patient samples, due to the time and labour constraints of manually examining a large volume of documents and searching for relevant information. Furthermore, such studies have often focused on specific patient samples, such as inpatients (Waddington et al. 1998; Centorrino et al. 2004), thus limiting the generalizability of their findings to wider and more diverse patient populations. In this thesis, I successfully used a combination of NLP and a bespoke algorithm to extract antipsychotic polypharmacy data from a large, but nevertheless information-rich dataset, including free-text clinical notes. Mental health professionals often write some of the most relevant information in free text. In addition these fields often receive entries from different professionals and tend to contain the most up-to-date information (Perera et al. 2016). Therefore, from a data-derivation point of view, this thesis demonstrates the utility of using a novel way of extracting and examining medication data, where information can be derived from both structured and free-text fields. The migration from paper to electronic records has already begun in UK health services and internationally, in countries such as Sweden, Finland and Denmark. Therefore, this tool has the potential to be applied in similarly structured clinical datasets where a large proportion of medications data is held in free-text format. Furthermore, using similar methods across research to derive medication prescription information has the potential to overcome some of the most significant methodological problems that existing research has faced, such as assessing and measuring long-term antipsychotic polypharmacy. At

present, it is almost impossible to compare findings across studies due to significant differences in defining and measuring antipsychotic polypharmacy.

9.3.2 Who is prescribed antipsychotic polypharmacy?

Prior research has predominantly considered characteristics of patients prescribed antipsychotic polypharmacy (Suokas et al. 2012; Santone et al. 2011; Kreyenbuhl et al. 2007; Kreyenbuhl et al. 2006), rather than predictors of this regimen, mainly due to difficulties with determining prior episode of polypharmacy prescribing (Ganguly et al. 2004; Morrato et al. 2007) and the use of cross-sectional methods to investigate this (Suokas et al. 2012; Santone et al. 2011; Ortiz et al. 2016). Furthermore, studies to date have examined a limited number of possible predictors (Suokas et al. 2012; Ortiz et al. 2016; Ganguly et al. 2004; Gallego et al. 2012); therefore for example relatively little is known about the socioeconomic predictors, such as social deprivation. In this thesis (Chapter 6), I measured a number of socio-demographic, socioeconomic, clinical and service use factors, and was able to measure these over periods prior to the initiation of long-term antipsychotic polypharmacy. Therefore, I was able to ascertain predictors rather than characteristics of antipsychotic polypharmacy prescribing.

Overall, the results from the studies described in this thesis indicated that patients prescribed antipsychotic polypharmacy were more likely to be younger, to be homeless, to experience more psychotic symptoms, and to have had more previous service use (prior outpatient contact, prior community

treatment orders, prior clozapine and/or LAI use) (see Chapter 6). The studies described in Chapter 7 and 8, further indicated that patients on polypharmacy were more likely to have problems with hallucinations and delusions, and more previous contact with services (as measured by time known to SLAM services; and inpatient and outpatient contact), in comparison to patients prescribed monotherapy. This suggests that certain patient groups are at a particular risk of receiving antipsychotic polypharmacy prescription. The implications of this finding are discussed in more detail in section 9.6 of this chapter.

The results largely support previous research which has indicated that prior service use, such as more frequent outpatient contact (Kreyenbuhl et al. 2007; Ganguly et al. 2004), previous use of LAI, and clozapine (Ganguly et al. 2004), are associated with an increased risk for longer term antipsychotic polypharmacy. However, contrary to some previous reports, I found no evidence to suggest that polypharmacy initiation is predicted by the number of days spent as an inpatient or number of different antipsychotics used (Barbui et al. 2006; Ganguly et al. 2004; Morrato et al. 2007) in the previous six months. It is possible that these discrepancies are due to differences in measuring antipsychotic polypharmacy (60 days or more in previous research as compared to six months or more in my studies). Furthermore, the aforementioned studies did not account for the effect of previous use of this regimen. Consequently, in previous research it has been difficult to establish with confidence whether the reported correlates were predictors or products of polypharmacy prescribing. An additional important issue to consider is that

studies conducted in the US that have investigated medication insurance databases (Ganguly et al. 2004; Morrato et al. 2007) may be limited by sampling bias. More specifically, as access to services is not uniform across hospitals in different states, and individuals pay to receive care, it is possible that identified patients from some hospitals are not representative of their catchment populations, and thus have limited generalizability.

My results also generated some novel findings. Deprivation level of area of residence emerged as the sole socioeconomic factor that predicted initiating long-term antipsychotic polypharmacy. This is in contrast with previous research in this field, which has predominately examined employment status (Barbui et al. 2006; Biancosino et al. 2005; Santone et al. 2011) and has found mixed results. Therefore, the role of socioeconomic factors such as deprivation warrants further investigation. Furthermore, this thesis has shed further light on the role of clinical symptoms in antipsychotic polypharmacy prescribing. The presence of significant hallucinations and/or delusions, as rated on the respective HoNOS sub-scale, emerged as the sole symptomatic predictor of long-term antipsychotic polypharmacy initiation. Previous research in this field has been mixed, with some studies reporting no associations between general psychopathology and long-term antipsychotic polypharmacy (Barbui et al. 2006; Gallego et al. 2012), whereas research examining inpatient samples (Biancosino et al. 2005) indicating an association with positive symptoms. Overall previous research has generally examined small population samples (Barbui et al. 2006; Biancosino et al. 2005; Moilanen et al. 2016), thus limiting the statistical power to detect an effect and

the generalizability of their findings. In contrast, I was able to examine clinical factors in a large, diverse and representative patient sample.

9.3.3 What are the effects of antipsychotic polypharmacy prescribing?

The studies described in this thesis are some of the first to investigate both clinical and health outcomes (Chapter 7 and 8) using EHRs for a large and diverse cohort, taking into account a range of possible confounders. The studies have generated findings which are more representative of patients with SMI, and that can be generalised beyond the context of this study (this potential strength is further discussed in section 9.4 under Strengths).

Overall, previous research investigating outcomes of polypharmacy has been of varying quality. Studies examining antipsychotic duration of 60 days (that can possibly include cross-titration) have risked possible misclassification (Katona et al. 2014; Boaz et al. 2013). In addition, studies have only investigated limited potential confounders (Katona et al. 2014; Tiihonen et al. 2012), such as antipsychotic dose, as a result of having access to limited contextual information, thus possibly risking residual confounding (Katona et al. 2014; Tiihonen et al. 2012). While some smaller studies that examined polypharmacy of unspecified duration have been able to account for more contextual factors (Waddington et al. 1998; Joukama et al. 2006), smaller samples increase the likelihood of making a type II error and increase the likelihood that the findings are spurious.

The results of this thesis suggest that polypharmacy has significant clinical repercussions in comparison to monotherapy. More specifically, patients discharged on antipsychotic polypharmacy were more likely to be readmitted into hospital within six months in comparison to those discharged on monotherapy. The results appeared robust and remained after adjusting for a multitude of potential confounders, after carrying out sensitivity analyses, and after using propensity score methods to address confounding by indication. Overall, previous research in this field has been sparse and has provided mixed evidence of the role of polypharmacy in hospital readmissions. My results support findings from studies that have used clinical records to examine hospitalization [(Kreyenbuhl et al. 2007)(investigated antipsychotic polypharmacy of unspecified duration and therefore did not qualify for the literature review in this thesis)]. On the other hand, research using medical insurance databases have indicated that polypharmacy is associated with either a decrease in hospital readmissions (Katona et al. 2014) or is not associated with future hospital readmissions; rather readmission was associated with patients being insufficiently stable at the point of initial discharge (Boaz et al. 2013). Clinical severity in patients prescribed antipsychotic polypharmacy (Correll & Gallego 2012; Ganguly et al. 2004; Kreyenbuhl et al. 2007) is one possible explanation proposed for the higher level of readmission in comparison to patients on antipsychotic monotherapy. However, it is also possible that findings from insurance databases are subject to residual confounding, due to limited number of factors examined (Katona et al. 2014)(such as dose or smoking) and sampling bias as a result of inequality in access to services (Boaz et al. 2013). Furthermore, an

important caveat in the latter studies (Katona et al. 2014; Boaz et al. 2013) is that misclassification of polypharmacy cannot be completely ruled out as a result of examining antipsychotic polypharmacy with a duration of 60 or more days.

I found modest evidence to suggest that antipsychotic polypharmacy is associated with higher all-cause mortality. This finding does not clearly contradict or support previous studies. Research that has examined antipsychotic polypharmacy of unspecified duration in clinical records has reported that antipsychotic polypharmacy significantly increased the risk of mortality (Waddington et al. 1998; Joukama et al. 2006). On the other hand, results from larger and more diverse cohorts have indicated that antipsychotic polypharmacy either decreases the risk for mortality (Katona et al. 2014), or has no association with all cause and natural cause of death (Baandrup et al. 2010; Tiihonen et al. 2009; Tiihonen et al. 2012). However, the lack of contextual data available to examine potential confounders in more recent research (Tiihonen et al. 2012; Katona et al. 2014) has left a doubt over whether this holds true. Therefore, in the study described in Chapter 8, I sought to adjust for a range of factors such as socio-demographic, socioeconomic, and service use. In addition, by using propensity score methods, I sought to address confounding by indication to some extent.

This thesis has generated several novel findings in relation to antipsychotic polypharmacy and mortality. In line with evidence from previous descriptive research, patients receiving antipsychotic polypharmacy were more likely to

receive a higher combined antipsychotic dose (Gisev et al. 2014; Grech & Taylor 2012; Roh et al. 2013; Roh et al. 2015). However, there has been no previous research that has adjusted for dose in examining the association between long-term antipsychotic polypharmacy and mortality. I found no evidence to suggest that antipsychotic dose had a direct effect on mortality. Although this is at odds with previous research examining the association between antipsychotic dose and mortality (Torniainen et al. 2015; Ray et al. 2009; Osborn et al. 2014), it is important to note that the methods used to measure dose appeared to play a pivotal role in the final results. More specifically, in my study, the effect of dose was only evident when I examined dose as percentage of the maximum BNF recommended dose, and this was not sustained for olanzapine equivalent dose. Although I cannot definitively conclude that antipsychotic dose does not have an effect on mortality, given previous research, it is imperative to consider the limitations of existing methods used to measure dose. For example, methods such as BNF dose and defined daily dose calculate dose by using the upper licensed dose range of antipsychotics (Patel et al. 2013). This poses a problem for antipsychotics that reach their maximum efficacy at a lower dose range, such as risperidone, and thus are rarely prescribed at maximum or above maximum recommended dose. Furthermore, over the years, there have been reductions to the recommended maximum doses for some antipsychotics. Thus it is difficult to compare findings from different studies across time. An alternative explanation for differences in findings across studies is the possibility of residual confounding. For example, although Torniainen et al. (Torniainen et al. 2015) used age and gender matched case and controls, the Cox model did

not account for any other factors that may affect mortality such as smoking, which is associated with significant risk for death in people with SMI (Goff et al. 2005; Brown et al. 2000) although, as discussed previously, there may be issues of over-adjustment in instances where smoking behaviour is a consequence of prescribing practices. This study highlights an important issue around measuring antipsychotic dose and investigating its role in the association between polypharmacy and death. Future research in this field would greatly benefit from a 'gold standard' method of dose equivalence and measurement, thus facilitating across-study comparisons.

9.4 Strengths

The studies described in this thesis had several strengths, most of which are also mentioned in the respective chapters. SLAM is close to being a monopoly mental health care provider for its geographic catchment. Therefore, routinely collected EHRs capture a range of populations, such as patients in different clinical settings (e.g. inpatients/ outpatients). In addition, CRIS is based on an 'opt out' system and to date only three patients (Perera et al. 2016) have asked for their records to be removed from the search system, and as a result the coverage is close to 100%. Furthermore, routine mortality tracing and linkages with the Office of National Statistics national mortality ensures that if a death occurs within the UK, even if it is outside SLAM catchment, this information will be fed back to the service. Consequently, I was able to capture and follow-up a large cohort of patients with SMI, which was representative of patients seen by secondary care (Stewart et al. 2009; Perera et al. 2016).

EHRs contain rich and diverse contextual information, much of which may be embedded in free-text fields. Thus, in comparison to previous research (Suokas et al. 2012; Ortiz et al. 2016; Ganguly et al. 2004), I was able to incorporate relatively detailed information on socio-demographic, socioeconomic, clinical and service use factors, some of which have been previously under-represented and/or under-investigated, such as ethnicity and level of deprivation. Furthermore, the size of the sample I investigated gave me the statistical power to adjust for multiple potential confounders in the analysis, thus limiting residual confounding. In addition, having rich contextual information (such as socioeconomic factors and antipsychotic dose), allowed me to distinguish with a better precision between different types of antipsychotic polypharmacy, thus limiting potential misclassification (Chapter 4 and 5), a problem that a large proportion of previous research has been unable to avoid (Centorrino et al. 2004; Joukama et al. 2006; Ito et al. 2005; Misawa et al. 2011; Sim et al. 2004; Janssen et al. 2005). Misclassification was further reduced by using a combination of NLP and the novel algorithm described in Chapter 5. This allowed me to extract information available in structured fields and free text. In instances where structured fields are poorly populated or incomplete, using supplementary information available in free-text fields provides more detailed and complete data on treatments. A further advantage of NLP is its ability to take into account the linguistic context around terminology of interest. I was able to identify and exclude negation statements, past rather than current prescribing, speculations about future prescribing and instances in the text where the drug is mentioned as being

taken by a person other than the patient, thus further increasing the precision of identifying antipsychotic polypharmacy.

EHRs reflect real-life clinical practice and have an advantage over randomised control trials and clinical cohort studies, which often suffer from poor response rates and loss to follow-up. Furthermore, randomised controlled trials are often restrictive in their inclusion criteria (e.g. comorbid diagnoses); operate in idealized environment (e.g. number of clinical contacts); and have short follow-up period, making it hard to investigate rare outcomes such as mortality that require longer follow-up. Therefore, EHRs offer an invaluable tool for investigating trends in medication prescribing and the impact of medications under real-world circumstances that are not necessarily captured by clinical trials. As a result, EHRs have the potential to provide valuable information that can inform prescribing guidelines.

The historic nature of EHRs allows longitudinal research, where medication profiles can be examined in relation to multiple predictors and outcomes. Although EHRs provide historical information, recall bias is rarely an issue, as records are entered close to the time the events occur. For example, in Chapter 6, measuring predictors prior to antipsychotic polypharmacy initiation allowed me to separate the exposures and outcome in time, thereby reducing the potential for reverse causality.

At present, there is no ‘gold standard’ for calculating equivalent antipsychotic doses (Patel et al. 2013), therefore I chose to use two different methods in

Chapter 8. Percentage of the maximum BNF recommended dose has been recommended by the Royal College of Psychiatrist (Royal College of Psychiatrists 2014) as one method of choice for calculating high dose prescribing in polypharmacy. However, the olanzapine equivalence dose method has gained popularity in recent years (Gardner et al. 2010; Gisev et al. 2014; Patel et al. 2013) in this field, and is currently preferred to chlorpromazine equivalence. Furthermore, using two different approaches allowed me to test the effect of dose more rigorously and also demonstrate that existing evidence in this field needs to be interpreted with caution, as findings are possibly dependent on the method that is used.

I chose to compare antipsychotic polypharmacy to monotherapy treatment with a minimum duration of six months, as the reference group, therefore ensuring that all patients that qualified for the study were known to services for a minimum period. In Chapter 8, as well as using the propensity score method (discussed above), I carried out extra analysis to ensure that I had chosen the most appropriate reference group. In an addition to the main analysis, I compared the polypharmacy group: to patients with an episode of monotherapy in 2010 (appendix C); and to the rest of the sample (patients who did not qualify for the polypharmacy group)(appendix D).

9.5 Limitations

There were several potential limitations faced by the studies described in this thesis, also described in respective chapters. Despite adjusting for multiple

confounders, it is possible that some residual confounding may have occurred in studies described in Chapters 6, 7 and 8. For example, I was unable to measure factors such as duration of illness or stages of treatment as patients entered the observation period. In addition, I was unable to measure clinician related factors such as prescriber experience of initiating antipsychotic polypharmacy (Correll et al. 2011; Correll & Gallego 2012; Gee et al. 2014). Although I employed propensity score as both a covariate and in a sensitivity analysis in Chapters 7 and 8, where I restricted the analysis to patients that could have been prescribed either monotherapy or polypharmacy, confounding by indication cannot be completely ruled out. Interaction with calendar time was not measured in Chapter 7 and Chapter 8. Therefore it is possible that risk may have varied over calendar time.

Despite examining a large and diverse clinical cohort, the possibility of not having sufficient power to examine rare outcomes such as mortality remains. In Chapter 8, I observed a modest effect of long-term antipsychotic polypharmacy on all-cause and natural causes of death. This association was significant in only some models. However the effect size changed little across the different models which may suggest that non-significance in some models may have been due to lack of power rather than confounding.

In contrast to previous research where standardised symptomatic assessments have been used (e.g. PANSS, BPRS), symptom assessment in Chapter 6 and 7 was limited to individual HoNOS items, measured at one point in time. This scale has received some previous criticism with regards to

its measurement of symptoms (Stein 1999; Bebbington et al. 1999), and I was only able to analyse a composite measure of psychotic symptoms. It is possible that true associations may have been concealed, and further research is required into the role of observed and recorded symptomatology in clinical decision-making.

Despite examining the specific effects that certain antipsychotics, such as clozapine or groups of antipsychotics such as FGAs, could have had on the overall associations of interest, examining the effects of a broad range of specific combinations of antipsychotics was beyond the scope of the studies (Chapter 7 and 8). It is therefore possible that the risk for detrimental outcomes such as mortality, differs across certain combinations of antipsychotics (Kiviniemi et al. 2013; Hayes et al. 2014; Montout et al. 2002; Tenback et al. 2012).

There were several limitations specific to the use of EHRs. For example, as a secondary dataset, I was not able to insert variables that I may have wanted to investigate; rather I had to work with the data that were available. In addition, the completion of certain information by clinicians is beyond the control of the researchers. Therefore some variables had a large proportion of missing values and could not be included in the analysis. Furthermore, in the analysis I was unable to account for unmeasured/ unrecorded confounding factors. For example, it is possible that there is a systematic bias in record keeping across the EHRs, where oral and depot medication are recorded differently. Outpatients receiving a combination of oral and depot medication

may not be identified as antipsychotic polypharmacy. Although for depot injections the patients are often required to return to the outpatient clinic to have it administered, they can obtain repeat prescriptions for oral medications by their GP. Therefore, as CRIS reflects secondary care records, I potentially may have only been able to detect the administration of depot and therefore misclassify the patient as receiving monotherapy.

9.6 Implications

The results from Chapter 6, 7 and 8 suggest that patients prescribed antipsychotic polypharmacy are likely to be already experiencing significant burden prior to and as a result of antipsychotic polypharmacy. For example, patients initiated on antipsychotic polypharmacy are more likely to be from a more deprived area and more specifically homeless (based on area socioeconomic deprivation index), to experience significant problems with positive clinical symptoms and to have had more previous mental health service use. At present there is little evidence to indicate that antipsychotic polypharmacy is more effective than monotherapy regimens (Galling et al. 2017). In fact, the high level of inpatient readmission (Chapter 7) can be interpreted as an indicator that polypharmacy is not effective in managing mental health symptoms in the community. In addition previous research has indicated that antipsychotic polypharmacy is associated with more side effects, and side effects of greater severity (Barbui et al. 2016; Gallego et al. 2012; Correll et al. 2007; Langan & Shajahan 2010) than antipsychotic monotherapy; therefore, further contributing to treatment burden experienced by this group of patients.

My findings that certain patient groups are at an increased risk for long-term antipsychotic polypharmacy initiation have important treatment implications. For example, clinicians can pay particular attention to factors that are known to predict antipsychotic polypharmacy (Chapter 6) earlier on in the treatment process, and perhaps employ a broader range of interventions in addition to pharmacotherapy, to reduce the risk of antipsychotic polypharmacy prescribing in the future. Mace and Taylor (Mace & Taylor 2015) indicated that antipsychotic high doses and polypharmacy can be reduced through regular patient reviews and collaborative work between clinicians and pharmacists. Their quality improvement programme managed to successfully reduce the rate of polypharmacy from 57% to 16% in inpatient settings and intensive care units. This was clearly a substantial decrease and suggests that even though some patients may be more likely to be prescribed polypharmacy, this is not necessarily a long-term treatment management strategy and can be successfully transitioned to monotherapy.

My findings further indicate that only a third of the patients initiated on antipsychotic polypharmacy had previously been trialled on clozapine (Chapter 6). This has been previously suggested (Howes et al. 2012; Nielsen et al. 2012), and highlights that prescribing guidelines (e.g. that antipsychotic polypharmacy should only be considered after trials of two individual agents followed by clozapine) are not consistently applied in 'real-world' clinical practice. However, it is important to note I was unable to establish reasons for not prescribing clozapine and therefore it is possible that a proportion of

patients could have refused this treatment. In cases where antipsychotic polypharmacy has been initiated prior to the clinician considering clozapine Barnes and Paton (Barnes & Paton 2011a) have suggested that to modify premature polypharmacy prescribing, services may need to implement a combination of treatment algorithms, educational outreach, standardised assessments of symptoms and adverse effects and examine specific local barriers to change.

My findings also have important service implications. The high prevalence of hospital readmissions amongst patients discharged on antipsychotic polypharmacy supports previous research which has indicated that antipsychotic polypharmacy is associated with significantly increased service costs due to higher bed occupancy and length of inpatient stay, as well as the extra costs associated with multiple medication prescribing (Baandrup et al. 2012; Gilmer et al. 2007; Valuck et al. 2007). Therefore, reducing antipsychotic polypharmacy prescribing may have benefits at both the patient and service level.

9.7 Possible mechanisms and future research

9.7.1 Adverse drug reactions

Approximately sixty per cent of the excess mortality in patients with schizophrenia is attributed to physical illnesses (Barnes et al. 2007). Antipsychotic pharmacotherapy has been associated with a number of physical health problems such as weight gain, diabetes, metabolic syndrome,

dyslipidaemia and prolonged QT and PR intervals (Auquier et al. 2006; Raedler 2010; Suzuki et al. 2014; Pramyothin and Khaodhiar 2010). These findings are most prominent for atypical antipsychotics. For example, olanzapine has been linked to an increased risk for weight gain and consequently metabolic problems (Leucht et al. 2009). Although some research suggests that this is most evident in young, treatment-naive patients (Pramyothin & Khaodhiar 2010), research using such samples is sparse; therefore this cannot be supported conclusively (Reynolds & Kirk 2010). Clozapine has been associated with diabetes mellitus (Newcomer 2014), pulmonary embolism (Hägg et al. 2000) and myocarditis (Killian et al. 1999).

In Chapter 6, I described how antipsychotic polypharmacy prescribing is likely to be a by-product of a complex interplay between a number of different patient, treatment and contextual factors. It is possible that similarly, the relationship between long-term antipsychotic polypharmacy treatment and death in patients with SMI is complex and subject to an interplay between a number of different factors. More specifically, it is possible that antipsychotic regimens, and more specifically polypharmacy, could increase the risk of certain side effects, which in turn can increase the risk of death. However, this needs further examination by future research

Research examining the effect of polypharmacy on physical health outcomes has been limited. However, there is some evidence to indicate that, for example, risperidone and clozapine polypharmacy has been associated with elevated prolactin levels (Ganguly et al. 2004; Galling et al. 2016). Combining

atypical antipsychotics has also been related to arrhythmia, asthma and complicated diabetes (Ganguly et al. 2004), whereas cross-generation polypharmacy has been associated with myocardial infarction (Ganguly et al. 2004). Furthermore, there is evidence which indicates that atypical drugs may have an additive side-effect profile (Freudenreich & Goff 2002). For example, a Danish longitudinal cohort study (Kessing et al. 2010) found that the incidence of diabetes increased with the number of antipsychotics co-prescribed. However, at present there have been no studies that have investigated side effects of long-term antipsychotic polypharmacy and mortality; therefore, it is not possible to draw firm conclusions. It is also important to bear in mind evidence that does not support the above mechanism, indicating that antipsychotic treatment has no direct effect on physical health (Brown et al. 2000). Kuo and colleagues (Kuo et al. 2011) concluded that patients with SMI have a genetic predisposition for obesity and metabolic problems, which precedes the effects of antipsychotic medication. Furthermore, Correll and colleagues (Correll et al. 2007) found that polypharmacy was not independently correlated with metabolic abnormalities, which were instead associated with demographic, clinical and anthropometric factors. Therefore, future research should aim to investigate causal pathways to mortality, including physical illness and adverse drug reactions in relation to antipsychotic medication use and more specifically to antipsychotic polypharmacy.

9.7.2 Concomitant non-antipsychotic medication use

SMI patients have an increased risk for comorbid diagnoses such as substance use, depression and personality disorder (Kreyenbuhl et al. 2007; Ganguly et al. 2004). Furthermore, as mentioned earlier in this section, this population also has high physical health comorbidities (Auquier et al. 2006; Raedler 2010; Suzuki et al. 2014; Pramyothin & Khaodhiar 2010). Therefore it is likely that comorbid medication use may have some effect; possibly not so much on clinical outcomes such as readmission, but more so on physical health outcomes such as mortality.

A large Danish cohort study examining long-term antipsychotic polypharmacy and benzodiazepines has indicated that current use of benzodiazepines with a long elimination half-life (24hrs or more) is associated with increased risk of natural death in patients with schizophrenia (Baandrup et al. 2010). Similarly, a large Finnish study (Tiihonen et al. 2012) also indicated that benzodiazepine use is associated with all-cause mortality, and for suicidal and non-suicidal deaths in this population. Furthermore, the latter study also indicated that the concomitant use of antipsychotic polypharmacy with benzodiazepine and antidepressants is associated with increased risk for mortality in SMI. There has been some further evidence from one large US Medicaid study (Ganguly et al. 2004) and a meta-analysis (Gallego et al. 2012) investigating over 147 studies and over a million participants, that have indicated that mood stabilisers such as lithium and antidepressants are both associated with antipsychotic polypharmacy prescribing. Finally, the latter two studies have also indicated that anticholinergic agents (Gallego et al. 2012) and drugs for

physical health problems such as tuberculosis, hyperlipidaemia and cancer (Ganguly et al. 2004) are also associated with long-term antipsychotic polypharmacy prescribing. Therefore, it is possible that the other non-antipsychotic concomitant medication use could have a confounding effect on the association between long-term antipsychotic polypharmacy and mortality. To better understand the risk of mortality in SMI, we may need to investigate medications used for physical illness and other psychotropic medications in addition to antipsychotics.

9.7.3 Effects of individual antipsychotics or specific antipsychotic combinations

Although in this thesis I did not have the ability to investigate all antipsychotic combinations individually, I tested for the effect of specific antipsychotic (e.g. clozapine) and/or combinations (e.g. FGAs) where possible (see Chapter 7 Table 7.4 and Chapter 8 section 8.7). As previously discussed, antipsychotics such as clozapine have been associated with reduced hospitalisation and mortality, whereas most FGAs, whether as part of polypharmacy or not, have been associated with higher risk for mortality (Chapter 7, section 7.2; Chapter 1 section 1.3). Although evidence on SGAs have been mixed, antipsychotics such as olanzapine have also been associated with increased mortality, especially from natural causes (e.g. cardiovascular)(see Chapter 1 section 1.3). As a result, it is possible that specific antipsychotics and/or combinations may exhibit different effects on outcomes such as hospital readmission into secondary mental health care and mortality. Therefore, future research could

focus in more detail on examining common antipsychotic combinations and their effect on clinical and health outcomes in the SMI population.

9.8 Conclusions

The studies described in this thesis are, I believe, some of the first to investigate both predictors and outcomes of long-term antipsychotic polypharmacy prescribing in secondary mental health care in patients with SMI. More specifically, I examined an array of possible predictors (Chapter 6) and both clinical and health outcomes (Chapter 7 and 8) extracted from EHRs for a large, diverse and representative cohort, thus increasing the generalizability of my findings. In addition, I measured and adjusted for a multitude of possible confounders, thus reducing residual confounding.

Overall, this thesis provides evidence that EHRs, such as SLAM de-identified health records (CRIS), can be successfully used to derive information on long-term antipsychotic polypharmacy prescribing in secondary mental health care with high precision (Chapter 5). My findings further indicated that certain sub-groups in the SMI population, such as patients who are younger, homeless, having significant problems with clinical symptoms, and greater previous service use, could be at increased risk of receiving long-term antipsychotic polypharmacy treatment. As discussed in section 9.6 of this chapter, these findings could have important treatment implications, specifically for unwarranted cases of polypharmacy (such as those where clozapine has not been previously trialled) by increasing clinicians' awareness to pre-empt antipsychotic polypharmacy prescribing.

In addition, my results indicated that patients prescribed long-term antipsychotic polypharmacy at discharge were at increased risk for clinical outcomes such as hospital readmission into secondary mental health care (Chapter 7). Lastly, I found insufficient evidence to indicate that antipsychotic polypharmacy prescribing is associated with statistically significant increase in the risk for all-cause mortality for patients with SMI (Chapter 8). Overall, it is likely that patients prescribed antipsychotic polypharmacy suffer considerable burden, whether or not this is directly caused by this regimen. As discussed in section 9.6 of this chapter, this has clinical and treatment implications. More specifically, although a proportion of these patients under the guidance of existing recommendations, would require antipsychotic polypharmacy, the justification behind the prescription of this regimen where it is unwarranted, needs specific attention. A recent clinical programme in SLAM (Mace & Taylor 2015) indicated that antipsychotic polypharmacy can be successfully reduced by clinicians and pharmacists closely collaborating and reviewing cases of polypharmacy. Therefore, similar programmes need to become a priority, in clinical settings with high antipsychotic polypharmacy prescribing.

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APPENDIX A

Publications in peer-reviewed journals

Kadra, G., Stewart, R., Shetty, H., Jackson, R. G., Greenwood, M. A., Roberts, A., Chang, C.-K., MacCabe, J. H., and Hayes, R. D. (2015). Extracting antipsychotic polypharmacy data from electronic health records: developing and evaluating a novel process. *BMC Psychiatry*, *15*(1), 166. doi:10.1186/s12888-015-0557-z

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BMC Psychiatry

RESEARCH ARTICLE Open Access

Extracting antipsychotic polypharmacy data from electronic health records: developing and evaluating a novel process

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Abstract

Background: Antipsychotic prescription information is commonly derived from structured fields in clinical health records. However, utilising diverse and comprehensive sources of information is especially important when investigating less frequent patterns of medication prescribing such as antipsychotic polypharmacy (APP). This study describes and evaluates a novel method of extracting APP data from both structured and free-text fields in electronic health records (EHRs), and its use for research purposes.

Methods: Using anonymised EHRs, we identified a cohort of patients with serious mental illness (SMI) who were treated in South London and Maudsley NHS Foundation Trust mental health care services between 1 January and 30 June 2012. Information about antipsychotic co-prescribing was extracted using a combination of natural language processing and a bespoke algorithm. The validity of the data derived through this process was assessed against a manually coded gold standard to establish precision and recall. Lastly, we estimated the prevalence and patterns of antipsychotic polypharmacy.

Results: Individual instances of antipsychotic prescribing were detected with high precision (0.94 to 0.97) and moderate recall (0.57-0.77). We detected baseline APP (two or more antipsychotics prescribed in any 6-week window) with 0.92 precision and 0.74 recall and long-term APP (antipsychotic co-prescribing for 6 months) with 0.94 precision and 0.60 recall. Of the 7,201 SMI patients receiving active care during the observation period, 338 (4.7 %; 95 % CI 4.2-5.2) were identified as receiving long-term APP. Two second generation antipsychotics (64.8 %); and first -second generation antipsychotics were most commonly co-prescribed (32.5 %).

Conclusions: These results suggest that this is a potentially practical tool for identifying polypharmacy from mental health EHRs on a large scale. Furthermore, extracted data can be used to allow researchers to characterize patterns of polypharmacy over time including different drug combinations, trends in polypharmacy prescribing, predictors of polypharmacy prescribing and the impact of polypharmacy on patient outcomes.

Keywords: Antipsychotic polypharmacy, Electronic health records, Precision, Recall

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Background

Clinical health records have been previously used to examine antipsychotic medication prescribing [1, 2]; however, the potential value of electronic health records (EHRs) remains underexplored. In the context of mental health care, EHRs contain large volumes of detailed information in free-text and structured fields, providing an important resource for conducting analyses using large samples and investigating a multitude of patient characteristics and outcomes simultaneously [3].

Studies investigating prescription databases [4–6] have been successful in deriving medication data for large populations and over long periods of time by predominately extracting data from structured fields (such as drop down menus, or dedicated response boxes) [6]. However, such studies have been restricted by the limited nature of the derived information [7]. Data on drug prescription, as well as related contextual information, is frequently embedded in free-text fields in mental health EHRs and this may be the only source of such information in the absence of e-prescribing or a Primary Care linkage. Traditionally, extracting free-text information has necessitated manual coding (where a researcher reads free-text and codes it by hand according to a defined set of coding rules) [8], which is time and labour intensive and therefore, not always feasible on a large scale. This can result in investigating a smaller than ideal sample [9–12]. EHR text has been analysed automatically using techniques such as natural language processing (NLP) for a variety of purposes [13]. However, although this has involved the identification of drugs [14], as far as we are aware, there have been no attempts to develop and validate techniques for characterising meta-data such as polypharmacy.

Automated extraction of information on medication prescribing is potentially valuable for investigating specific but important, clinical prescribing patterns such as the practice of prescribing more than one antipsychotic drug simultaneously, known as antipsychotic polypharmacy (APP), which may be challenging to identify through manual searches. The prevalence of APP in routine clinical practice has been estimated to vary between 10-30 % [15] in people with serious mental illness (SMI), despite little empirical evidence to support benefits associated with its use [16], and associations with adverse health outcomes, such as increased physical health problems (i.e. weight gain, diabetes, metabolic syndrome, dyslipidemia) and mortality [17–19]. We need to gain a better understanding of the clinical characteristics that predict APP prescribing and determine associated health outcomes. This information might be provided through research using the more "real-life" data present in EHRs. APP is thus an important exposure and potential confounder to be considered in studies investigating the impact of antipsychotic drugs in clinical settings and yet, as stated, is difficult to characterise on a large scale.

In this paper, we present and evaluate a novel process of extracting APP data from a large EHR data resource, utilising information available from both structured and free-text fields. In addition, we were able to use the processed data to estimate the prevalence of APP, as well as patterns in co-prescribing, for a six-month period in 2012.

Methods

Settings

South London and Maudsley NHS Foundation Trust (SLAM) is one of the largest providers of secondary healthcare in Europe, serving a geographic catchment of 1.23 million residents across four London boroughs (Lambeth, Southwark, Lewisham and Croydon) [20]. EHRs have been used by SLAM in all its services since 2006. In 2008 The Clinical Record Interactive Search (CRIS) system was developed [20], which allows researchers to search and retrieve anonymised SLAM EHRs, with over 230,000 cases currently represented in the system. CRIS was approval by the Oxfordshire Research Ethics Committee C (reference 08/H606/71).

Sample

All adult service-users with a serious mental illness (SMI) diagnosis of schizophrenia (ICD-10: F20), schizoaffective disorder (F25) or bipolar disorder (F31) who received care from SLAM between January and June 2012 were considered. Diagnostic data were derived from free-text and structured fields within CRIS.

Deriving antipsychotic polypharmacy data from EHRs

All antipsychotic drugs listed in the British National Formulary (BNF) 65 were considered. The BNF is a reference book containing information on pharmacology and prescribing of many medicines (including 29 antipsychotics) available on the British National Health Service (NHS). Structured fields for recording medications data are present in the source EHR interrogated by CRIS, and were used in this analysis, but these are infrequently completed. Information was also extracted from SLAM pharmacy records, although this only covers particular drugs that are subject to monitoring by the pharmacy such as clozapine. Most antipsychotic prescription information was extracted from free-text fields, including those recording clinician-patient encounters, and correspondence between healthcare professionals.

We extracted antipsychotic medication data from the free-text with a NLP information extraction application developed using General Architecture for Text Engineering (GATE) software [21], a suite of tools that facilitates the use and development of NLP applications and features. We applied NLP to extract a variety of grammatical

features, which in turn were used to create specific filters to maximize precision and recall on instances of antipsychotic prescribing. For example, all instances of medication prescription that were not prescribed at the 'present time' (this refers to medication prescribed up until today, or from today with regard to the date the document was written) and that did not include a dose value were excluded at the point of data extraction. Therefore, any mentions of the drug without such supporting prescription information were not extracted, as these were deemed too imprecise.

APP algorithm

Long-term APP was defined as the concomitant use of two or more antipsychotics for six or more months. We considered that a concomitant use of antipsychotics for a six months duration reduces the possibility of misclassifying brief periods of co-prescribing during switching (a practice known as cross-titration, which typically takes up to 10 weeks [16, 22]) and 'as required' prescriptions as long-term APP; although, our approach cannot absolutely exclude cross-titration that has taken unusually long [16, 23].

APP was ascertained using an algorithm comprising of two steps, as illustrated by Fig. 1. In step one, case records were examined to determine whether two or more antipsychotics were prescribed within a six-week period between January and June 2012. Co-prescribing at this stage (t0) was defined as baseline polypharmacy. At stage two, data on all patients with APP at baseline were re-examined six months after t0. A manual inspection of the data revealed that we were initially omitting outpatients who had less frequent clinical appointments and longer periods of time with no entry in the clinical record. Consequently, we specified that the follow-up search should begin at the point of first clinical event occurring six months or more after t0, which we designated as t1. Antipsychotic information was extracted from the clinical records, for the first ten weeks following t1, to determine whether the same set of antipsychotics were prescribed; if so, this was classified as 'long-term' polypharmacy.

During further development of the algorithm, we established that NLP-derived time and dose features were not sufficient to identify cases of APP, as they were not able to completely exclude historic medication information in clinical summaries, resulting in false positive instances (this refers to cases that are not true polypharmacy, but are detected as such by the application). Therefore, two additional filters were devised, applying the following exclusions: i) antipsychotic drugs with only a single annotation (by *annotation* we mean the identification and marking of spans of text that represent the prescribing of an antipsychotic) for the entire study period; and ii) antipsychotic drugs with multiple annotations but where all annotations were restricted to a single document for the entire study period. We reasoned that it was unlikely that a patient prescribed particular medication would have it mentioned in their notes only once over this period or only on a single day (i.e. a single document) over this period.

To evaluate the performance of the data extraction process (NLP application and APP algorithm), we measured two indicators of validity: precision and recall. Precision (equivalent to positive predictive value in psychometrics) represents the proportion of patients identified as polypharmacy considered to be 'true positive', out of all cases identified as such by the algorithm. Recall (equivalent to sensitivity) represents the proportion of patients on given medications who were identified as such by the algorithm.

Validation

Prior to testing the performance of the APP algorithm, we examined the NLP application on extracting information for specific antipsychotic agents prescribed at individual points in time (i.e. instances rather than episodes). The first author examined and manually coded free-text records over a 6-month period (January to June 2012) for a subset of 120 patients. We chose to

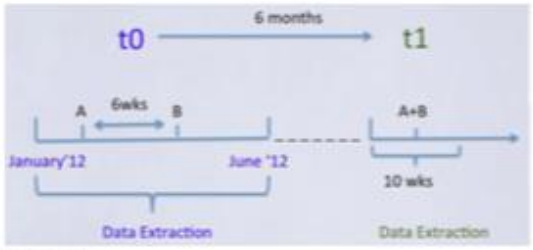

Fig. 1 Antipsychotic polypharmacy algorithm

examine six frequently prescribed antipsychotics [24] under the assumption that these medications would have a larger number of annotations for examination. Precision and recall for the extraction of clozapine prescriptions using this NLP algorithm is not included here as this has been described previously [25]. Consequently, the instances of antipsychotic prescribing varied from 328 to 1150 instances, by antipsychotic agent. We ran the NLP application over this set of unseen documents (that had not been used in the development of the NLP application) and compared the results to our manual coding of the same dataset.

As illustrated by Fig. 2, the final APP algorithm was derived following an iterative validation process. From those that were initially identified as being on polypharmacy by the application, we selected a random subset of 40 patients and manually coded their clinical records for APP, in order to ascertain its 'true' occurrence (also referred to as the 'gold standard'). The extracted data were then compared against the gold standard to ascertain the validity of APP and to examine discrepancies. Instructions within the algorithm were then added or edited accordingly until a satisfactory performance was obtained. To confirm generalizability, the 'final' algorithm was tested out on a new subset of 30 randomly selected patients. To estimate recall, from all patients active in the observation period, we selected a random subset of 110 individuals.

Analysis

Having assessed the precision and recall of the NLP application and APP algorithm, using the APP algorithm we estimated the prevalence of baseline and long term (≥6 months) APP. Prevalence estimates and 95 % confidence intervals were reported for baseline and long-term polypharmacy, as well as for long-term polypharmacy distribution by antipsychotic class and by individual agent.

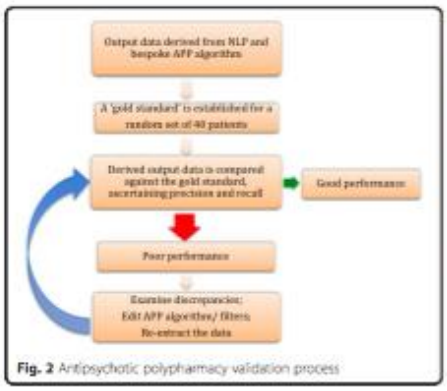

Fig. 2 Antipsychotic polypharmacy validation process

Results

As summarised in Table 1, the NLP application was able to identify individual instances of the selected antipsychotic agents with high precision, although recall levels were more modest. For the APP algorithm, the precision obtained from the final validation set of 30 patients was 0.92 for baseline and 0.94 for long-term APP. Recall was estimated at 0.74 and 0.60 for baseline and long- term APP respectively.

We determined that 7,201 adult patients with SMI diagnosis were active in SLAM services between January and June 2012. An estimated 830 (11.5 %; 95 % CI 10.8-12.3) patients were prescribed two or more antipsychotics in any six weeks between January and June 2012, and 338 (4.7 %; 95 % CI 4.2-5.2) were prescribed the same set of antipsychotics for six or more months.

Amongst patients prescribed long-term APP, co-prescribing two or more second-generation antipsychotics (SGAs) was most common (n = 219; 64.8 %; CI 95 % 59.7-69.9), followed by first generation (FGA) and SGA (n = 110; 32.5 %; CI 95 % 27.5-37.6) combinations, and two or more FGAs (n = 9; 2.7 %; CI 95 % 0.9-4.4).

Table 2 summarises long-term co-administration patterns by individual agents. Similarly to co-administration by class, the combination of two (or more) first generation antipsychotics (FGAs) was relatively rare. The most common antipsychotic used in combination was clozapine, combined with at least one other SGA.

Discussion

To our knowledge, this is the first report investigating the feasibility and yield for a process of extracting APP data from both structured and free-text fields in EHRs, using a combination of NLP and a bespoke algorithm. This process enabled us to identify instances where specific antipsychotic agents were prescribed, then classify baseline and long term APP profiles over time.

The NLP application combined with the APP algorithm performed at a high precision, suggesting that individuals classified as being prescribed APP were very

Table 1 Precision and recall per individual antipsychotic agent

Antipsychotic agent	N*	Precision (%)	Recall (%)
Amisulpride	619	97.4	61.0
Flupentixol	328	94.1	77.0
Haloperidol	747	94.0	57.0
Olanzapine	1150	95.0	69.3
Risperidone	737	95.0	64.1
Zuclopenthixol	390	97.0	67.5

*Number of annotations per antipsychotic

Table 2 Prevalence of long-term antipsychotic polypharmacy combinations (n = 338)

Antipsychotic medication	n	Plus at least one other FGA[a] n (%)	Plus at least one other SGA[a] n (%)
First Generation Antipsychotics (FGA)[a]			
Chlorpromazine	8	1 (12.5)	7 (87.5)
Flupentixol	26	6 (23.1)	20 (76.9)
Fluphenazine	4	2 (50.0)	2 (50.0)
Haloperidol	30	5 (16.7)	25 (83.3)
Levomepromazine	1	-	1 (100.0)
Pericyazine	1	1 (100.0)	-
Pimozide	2	-	2 (100.0)
Pipothiazine	10	2 (20.0)	8 (80.0)
Sulpride	33	1 (3.0)	32 (97.0)
Trifluoperazine	3	-	3 (100.0)
Zuclopenthixol	25	-	25 (100.0)
Second Generation Antipsychotics (SGA)[a]			
Amisulpride	118	18 (15.3)	100 (84.7)
Aripiprazole	79	12 (15.2)	67 (84.8)
Clozapine	168	27 (16.1)	141 (83.9)
Olanzapine	95	44 (46.3)	51 (53.7)
Paliperidone	40	8 (20.0)	32 (80.0)
Quetiapine	21	11 (52.4)	10 (47.6)
Risperidone	64	21 (32.8)	43 (67.2)

[a]These are overlapping categories; antipsychotic combinations may include additional FGAs or SGA where patients are prescribed more than 2 antipsychotics simultaneously

likely to be classified correctly. The moderate recall suggested that we were less able to detect all APP cases. In designing the APP algorithm, we noticed that some of the rules used to decrease the false positive cases of APP, filtered out some of the 'true' APP cases, requiring a trade-off decision. Although detecting all cases is desirable, especially when investigating relatively uncommon phenomenon such as polypharmacy, we chose to prioritise precision over recall due to the large number of non-cases in the sample, which might be expected to dilute the impact of any such misclassification in future analyses. Similarly, the NLP application was developed to favour precision over recall. In this study we considered date specific recall when evaluating the NLP application for extracting individual medications; however, in longitudinal studies a single patient often has a number of documents containing the same prescription information, therefore relatively low recall could be compensated by combining results extracted from several documents.

We estimated that just under five percent of all adult patients with SMI were prescribed two or more antipsychotics for six or more months. Although this is comparable to some research investigating APP with longer duration (Morrato et al. [26] found 6.4 % APP prevalence in Medicaid population), it is somewhat lower in comparison to other previous research (10-30 %) [15]. The lower prevalence could be attributable to a more conservative approach that was adopted in detecting APP, by examining long-term co-prescription with a minimum duration of six months. Some previous studies that have examined concomitant prescribing for 28 days [27], 6 weeks [28, 29] and 60 days [4, 30] may have included instances of 'as required' medication and switching. It is also possible that some polypharmacy cases were omitted because we prioritized precision over recall in developing the NLP application and algorithm. On the other hand, our findings are consistent with previous research on antipsychotic co-administration, where two or more SGAs, and FGA-SGA combinations are found to be the most prevalent combinations in clinical settings [15, 28, 29, 31, 32].

Previous research has suggested that olanzapine and risperidone are most commonly combined in co-prescribing [28, 33], whereas clozapine was the most commonly co-prescribed antipsychotic in our sample. Although the therapeutic benefits of clozapine co-prescribing has been previously called into question [34], this antipsychotic remains one of few that has some empirical support when used in polypharmacy [35]. Furthermore, most research to date has examined shorter periods of APP (i.e. 6 weeks) [28], whereas studies investigating long-term APP have reported a higher prevalence of clozapine as a component [4]. Clinically, this may indicate that patients persistently prescribed APP over longer periods of time are different from those on other forms of APP (i.e. short bouts of co-prescribing); more specifically, it is likely that this sub-group are more unwell and possibly treatment refractory [36].

Our process of extracting medication data from EHRs has a number of advantages. For example, in instances where structured fields are poorly populated or incomplete, using supplementary information available in free-text fields provides more detailed and complete information of treatments. A particular advantage of NLP is its ability to take into account the linguistic context around terminology of interest. Therefore, we were able to identify and exclude negation statements, past rather than current prescribing, speculations about future prescribing and instances in the text where the drug is mentioned as being taken by a person other than the patient. Furthermore, the APP algorithm allowed us to distinguish between different modes of polypharmacy administration, such as shorter (which would potentially include 'as required' and switching occurrences) and longer forms of co-prescribing.

Data from EHRs are a source of rich and diverse contextual information, much of which may be embedded

in free-text fields. The process described here, may be adapted to extract an array of factors, which may predict antipsychotic polypharmacy and/or confound associations between APP and mental or physical health outcomes. Routinely collected EHRs capture a range of populations, such as patients in different clinical settings (i.e. inpatients/outpatients) and with different socio-demographic profiles who have been previously been under-represented and/or under-investigated in research. Moreover, EHRs more closely approximate real-life clinical practice than formal research projects involving *de novo* data collection, permitting the identification of trends in medication prescribing that are not otherwise captured by clinical trials. This could be valuable information that can be fed back into prescribing guidelines. Finally, the historic nature of EHRs allows longitudinal research, where medication profiles can be examined in relation to multiple predictors and outcomes.

Our current protocol for extracted APP data has a number of limitations, which should be borne in mind. As indicated by the recall for individual antipsychotics and long-term antipsychotic polypharmacy, our approach may under-estimate the true prevalence of APP. Furthermore, the output data depends on the quality and accuracy of clinical entries [20], which may vary by clinicians and services. Finally, it is important to note that we examined antipsychotic polypharmacy over a relatively short period of time, and it is possible that our data reflects a specific pattern in medication prescribing during that period.

Conclusions

We have developed a novel process for extracting APP information from mental health electronic patient records. We have demonstrated that the combination of natural language processing and a bespoke algorithm can be an effective approach to extracting APP data. We were able to detect APP with high precision and modest recall. Once extracted these data can be used to allow researchers to characterize patterns of polypharmacy over time including different drug combinations, trends in polypharmacy prescribing, predictors of polypharmacy prescribing and the impact of polypharmacy on patient outcomes (such as mortality and physical health consequences). The use of NLP combined with a bespoke algorithm is likely to be applicable to similarly structured clinical datasets where medications data is held in free-text. Essentially we have provided an example of an approach which other researchers may trial in their own datasets with some modification to suit their specific needs and source data.

Abbreviations

APP: Antipsychotic polypharmacy; EHRs: Electronic health records; SLAM: South London and Maudsley; SMI: Serious mental illness; NLP: Natural language processing; CRIS: The Clinical Record Interactive System; BNF: British National Formulary.

Competing interests

RH, C-KC, RJ, HS, and RS have received research funding from Roche, Pfizer, J&J and Lundbeck. AR and MAG have received payment by BRC and Ontotext.

Authors' contribution

GK, RS, HS, RGJ, MAG, AR, C-KC, J-HM and RH have made substantial contributions to conception and design of the study. GK, RGJ and HS were involved in the acquisition of data. GK analyzed the data and RS, RH were involved in the interpretation of data. All authors have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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APPENDIX B

Publications in peer-reviewed journals

Kadra, G., Stewart, R., Shetty, H., Downs, J., MacCabe, J. H., Taylor, D., & Hayes, R. D. (2016). Predictors of long-term (≥ 6months) antipsychotic polypharmacy prescribing in secondary mental health care. Schizophrenia Research, 174, 1-3.

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Predictors of long-term (≥6 months) antipsychotic polypharmacy prescribing in secondary mental healthcare

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ABSTRACT

Introduction: The predictors of long-term antipsychotic polypharmacy (APP) initiation are poorly understood. Existing research has been hampered by residual confounding, failure to exclude cross-titration, and difficulties in separating the timing of predictors and APP administration.

Materials and methods: Using data from the South London and Maudsley (SLaM) case register, we identified all adult patients with serious mental illness (SMI) who were receiving care between 1st July 2011 and 30th June 2012. Exposures measured between 1st July and 31st December 2011 included socio-demographic, socioeconomic, clinical and service use characteristics. We then determined if long-term APP (six or more months) had been initiated between 1st January and 30th June 2012. Multivariable logistic regression models, adjusted for socio-demographic and socioeconomic factors, were built to investigate the associations between the above factors and the initiation of long-term APP.

Results: We identified 6857 adults with SMI receiving SLaM care, of whom 115 (1.7%) were newly prescribed long-term APP. In the adjusted models, predictors of long-term APP initiation included: symptoms (severity of hallucinations and/or delusions), previous treatments (clozapine and long-acting injectable antipsychotic agents), service use (more contact with outpatient services, community treatment order receipt), social factors (higher area-level deprivation, homelessness) and socio-demographic status (younger age, not in a relationship).

Conclusion: Our findings highlight that certain patient groups are at an increased risk for long-term APP initiation. Identifying these groups earlier in their treatment could encourage clinicians to employ a broader range of interventions in addition to pharmacotherapy to reduce the risk of APP prescribing.

1. Introduction

Antipsychotic polypharmacy (APP; the concomitant administration of two or more antipsychotics) remains common practice in treatment of serious mental illnesses (SMI). Its prevalence is estimated to vary between 10 and 30% (Freudenreich and Goff, 2002; Gallego et al., 2012), despite current guidelines recommending against APP use, except during clozapine augmentation (APA, 2004; Lochmann van Bennekom et al., 2013; NICE and NCCMH, 2013), and evidence of associations with increased mortality (Ganguly et al., 2004; Joukama et al., 2006; Waddington et al., 1998) and physical health problems (including metabolic and cardiovascular disorders) (Ganguly et al., 2004; Raedler, 2010). Examining factors that may predict APP prescribing is key to understanding its continued use.

To date, male gender (Ganguly et al., 2004; Kreyenbuhl et al., 2007a, 2007b; Morrato et al., 2007; Suokas et al., 2012), and younger age (Kreyenbuhl et al., 2007a, 2007b; Morrato et al., 2007; Suokas et al., 2012) have been found to be associated with APP, but there has been a lack of information on socioeconomic factors (Barbui et al., 2006). APP has been found to be associated with more frequent previous hospital admissions (Faries et al., 2005; Ganguly et al., 2004; Kreyenbuhl et al., 2007a, 2007b; Morrato et al., 2007), longer duration of previous admissions (Suokas et al., 2012), higher number of previous outpatient contacts (Ganguly et al., 2004; Kreyenbuhl et al., 2007a, 2007b) and previous antipsychotic medication use (Barbui et al., 2006; Ganguly et al., 2004). Findings regarding the role of clinical symptoms in APP prescribing have been inconsistent (Barbui et al., 2006; Biancosino et al., 2005; Centorrino et al., 2005).

Previous research has examined APP of varying duration (Broekema et al., 2007; Clark et al., 2002; Faries et al., 2005; Ganguly et al., 2004; Ito et al., 2005; Jaffe and Levine, 2003; Janssen et al., 2005; Misawa et al., 2011; Sim et al., 2004; Suokas et al., 2012; Taylor et al., 2002) and has often included polypharmacy during cross-titration, which has

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hampered definitive conclusions on predictors. More recently research has begun to investigate APP with longer duration (>60 days) in an attempt to distinguish between cross-titration and long-term treatment (Barbui et al., 2006; Faries et al., 2005; Ganguly et al., 2004; Kadra et al., 2015; Kreyenbuhl et al., 2007a, 2007b; Morrato et al., 2007). However, cross-titration is a process that can take up to 10 weeks to complete (Correll et al., 2011; Lochmann van Bennekom et al., 2013); therefore studies examining APP with a duration of 70 days or less cannot definitively exclude switching. Aside from heterogeneity in APP definition, investigations to date have risked residual confounding due to limited covariates in models (Centorrino et al., 2004; Faries et al., 2005). Furthermore, limitations in being able to distinguish temporally between the occurrence of APP prescribing and associated factors, makes it difficult to determine if the latter are predictors or consequences (Kreyenbuhl et al., 2007a, 2007b). Another limitation include small homogenous inpatient samples (Centorrino et al., 2004, 2005), restricting generalisability.

Using data derived from a large de-identified electronic health records case register with near-universal coverage of a defined population, we investigated socio-demographic, socioeconomic, clinical, and service-use predictors of long-term APP initiation in SMI.

2. Materials and methods

2.1. Study design, data source and study sample

This was a retrospective cohort study within a comprehensive register of patients treated with SMI in the South London and Maudsley (SLaM) NHS Foundation Trust. SLaM is one of the largest secondary mental health care providers in Europe, serving four London boroughs (Lambeth, Southwark, Lewisham and Croydon) and around 1.2M residents. As part of the National Health Service, SLaM is the universal provider of mental health services to this population. The Clinical Record Interactive Search (CRIS) was developed in 2008 and enables researchers to search and retrieve de-identified electronic health records (EHRs) information for over 250,000 service users in SLaM. The CRIS system has been described in detail (Perera et al., 2016; Stewart et al., 2009) and is approved by the Oxfordshire Research Ethics Committee C (reference 08/H606/71 + 5) as a database for secondary analysis.

Using CRIS, we ascertained all adult patients with a diagnosis of schizophrenia (ICD-10 code: F20.x), schizoaffective disorder (F25.x) or bipolar disorder (F31.x) and who were in contact with SLaM clinical services between 1st July 2011 and 30th June 2012. All potential predictors were measured prior to 1st January 2012. APP initiation was determined for the period between 1st January and 30th June 2012, also referred to as the follow-up period.

2.2. Outcome measures

The primary outcome was long-term antipsychotic polypharmacy (APP) initiation, defined as the concomitant prescription of two or more antipsychotic agents for at least six months, with the aim of minimising the likelihood of cross-titration. All service users who commenced APP at some point from 1st January to 30th June 2012, but who had not received APP in the 6 months prior to this were considered to have been 'initiated' on long term APP. A detailed account of the method used for APP ascertaining in CRIS and the validation of this technique have been described elsewhere (Kadra et al., 2015).

2.3. Explanatory variables

Age was calculated on the 1st January 2012 and categorised by quartiles. The remaining socio-demographic and socioeconomic factors were derived from the last entry recorded prior to 1st January 2012. Seventeen ethnic group categories were collapsed into "White", "Black Caribbean", "Black African" and "Other", due to small numbers in some cells. Relationship status was defined as "in a current relationship" (cohabitating, married or civil partnership) and "not in a relationship" (single, divorced, separated, widowed, unknown). Employment status was recorded as being in "paid employment" (part-time, full-time, self-employed) and "not in paid employment" (unemployed, registered disabled, retired, student, looking after children, volunteer, in training, not known, other). We used an area-level index of multiple deprivation to estimate socioeconomic status based on seven domains of deprivation ascertained from 2007 UK Census estimates (employment, income, education, health, barriers to housing and services, crime, and living environment), which are weighted and combined into an overall score applied to a given geographic area (DCLG, 2011). In this case, multiple deprivation indices were applied to lower super output areas (LSOAs), which are the smallest enumeration unit, each containing on average 1500 residents (DCLG, 2011). LSOAs were categorised in tertiles based on the four catchment boroughs. In addition, homelessness (Noble et al., 2008) was ascertained based on 'no fixed abode' codes.

Clinical symptom presence/severity was estimated from the most recent Health of the Nation Outcome Scale (HoNOS) completed prior to 1st January 2012. HoNOS is a clinical outcome instrument in wide routine use, composed of 12 items designed to measure behaviour, impairment, symptoms, and social functioning (Wing et al., 1998). Items are scored on a scale of 0 (no problem) to 4 (severe to very severe problem). Due to small cell sizes, subscale scores were collapsed into three categories: 0 "not a problem"; 1 "minor problem requiring no action"; 2–4 "significant problem" (Hayes et al., 2012). Items that provided overlapping information to other variables used in this analyses were removed; therefore we did not include item 9 (assessing relationship problems), item 11 (assessing living conditions) and item 12 (assessing occupational problems). Item 8 (assessing other mental health problems) was also excluded, as the following comorbid diagnoses were ascertained using information available from free-text and structured fields: i) depression [having received a diagnosis of depression (ICD-10: F32, F33) and/or scoring 'mild' to 'significant' on HoNOS item 7]; ii) substance use [having received a diagnosis of substance use disorder (ICD-10: F10–16) and/or scoring 'mild' to 'significant' on HoNOS item 3]; and iii) personality disorder [having received a diagnosis of personality disorder (ICD-10: F60; F61)].

We considered six measures of service use: i) previous outpatient contact was determined through the proportion of days each person had received face-to-face contact as an outpatient between 1st July and 31st December 2011 (multiple events on a single day were counted as one day of clinical contact, whilst clinical contact with outpatient services during an inpatient admission was not counted); ii) the number of days spent as an in-patient between 1st July and 31st December 2011 were determined separately; iii) we identified the number of previous antipsychotics used in the six months prior to follow-up; iv) we identified all patients who had received a community treatment order (CTO) prior to the start of follow-up [CTOs refer to a conditional discharge from inpatient admission, commonly implemented for a period of six months to improve adherence to medication and promote regular contact with services (DoH, 2007)]; dichotomous variables were generated to indicate whether, since 2007, patients v) had ever used clozapine or vi) ever used a long acting injectable (LAI) antipsychotic agent.

2.4. Statistical analysis

STATA 12 was used to conduct all statistical analyses. We estimated APP prevalence and incidence of newly initiated long-term APP in a six-month window. Further analyses focused on predictors of long-term polypharmacy initiation. Multivariable models included potential confounders such as age, gender, ethnicity, relationship status, employment, and deprivation status. Clinical and service use factors were not included as covariates due to possible over-adjustment for potential causal pathway factors.

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Several sensitivity analyses were carried out. Firstly, we tested whether the timing of the HoNOS assessment had an effect on the association between clinical items and APP initiation, by restricting the analyses to HoNOS scores obtained within the last year prior to the start of follow-up. We further tested whether being a local resident (as opposed to patients referred from the wider national catchment

Table 1
Cohort characteristics.

Variables	Total cohort N (%)	APP[a] N (%)	APP initiation[a] N (%)
Total sample	6857	331 (4.8)	115 (1.7)
Socio-demographic and socioeconomic factors			
Age			
16–35	1737 (25.3)	117 (35.3)	45 (39.1)
36–45	1789 (26.1)	105 (31.7)	31 (27.0)
46–55	1678 (24.5)	77 (23.3)	22 (19.1)
56+	1653 (24.1)	32 (9.7)	17 (14.8)
Gender			
Female	2821 (41.1)	111 (33.5)	40 (34.8)
Male	4036 (58.9)	220 (66.5)	75 (65.2)
Ethnicity group			
White	3124 (45.6)	125 (37.8)	41 (35.7)
Black Caribbean	992 (14.5)	54 (16.3)	16 (13.9)
Black African	1851 (26.9)	106 (32.0)	43 (37.4)
Other	890 (13.0)	46 (13.9)	15 (13.0)
Relationship status			
Not in a relationship	6052 (88.3)	311 (94.0)	111 (96.5)
In relationship	805 (11.7)	20 (6.0)	4 (3.5)
Employment status			
Not in paid employment	6521 (95.1)	326 (98.5)	113 (98.3)
In paid employment	336 (4.9)	5 (1.5)	2 (1.7)
Deprivation level in area of residence			
Low level	2087 (32.7)	95 (30.2)	25 (22.5)
Medium level	2111 (33.1)	113 (35.9)	40 (36.1)
High level	2107 (33.0)	97 (30.8)	42 (37.8)
Homelessness	74 (1.2)	10 (3.1)	4 (3.6)
Clinical factors			
Comorbid diagnosis			
Depression	3437 (50.1)	165 (49.9)	50 (43.5)
Personality disorder	895 (13.1)	63 (19.0)	20 (17.4)
Substance use	1956 (28.5)	103 (31.1)	38 (33.0)
Overactive and aggressive behaviour			
Not a problem	4127 (64.9)	198 (62.3)	64 (59.3)
Minor problem	1333 (21.0)	66 (20.8)	26 (24.0)
Significant problem	898 (14.1)	54 (16.9)	18 (16.7)
Non-accidental self-injury			
Not a problem	5850 (92.1)	292 (91.8)	100 (92.6)
Minor problem	326 (5.1)	20 (6.3)	5 (4.6)
Significant problem	179 (2.8)	6 (1.9)	3 (2.8)
Cognitive problems			
Not a problem	3799 (59.9)	181 (57.3)	64 (59.8)
Minor problem	1578 (24.9)	83 (26.3)	23 (21.5)
Significant problem	966 (15.2)	52 (16.4)	20 (18.7)
Physical illness or disability			
Not a problem	3502 (55.2)	175 (55.0)	57 (52.8)
Minor problem	1254 (19.8)	73 (23.0)	23 (21.3)
Significant problem	1591 (25.0)	70 (22.0)	28 (25.9)
Hallucinations and delusions			
Not a problem	2688 (42.3)	97 (30.5)	34 (31.5)
Minor problem	1314 (20.7)	74 (23.3)	25 (23.1)
Significant problem	2348 (37.0)	147 (46.2)	49 (45.4)
Problems with activities of daily living			
Not a problem	2842 (44.8)	121 (38.2)	44 (41.1)
Minor problem	1572 (24.8)	86 (27.1)	28 (26.2)
Significant problem	1934 (30.4)	110 (34.7)	35 (32.7)
Service use			
Days of inpatients stay in previous six months, mean ± SD (range)	11.8 ± 36.3 (0–184)	35.8 ± 60.0 (0–184)	18.8 ± 44.2 (0–184)
Days of outpatient contact in previous six months, mean ± SD (range)	9.4 ± 13.9 (0–174)	12.5 ± 15.1 (0–153)	12.2 ± 20.1 (0–153)
Previous CTOs			
No	6483 (94.6)	394 (88.8)	98 (85.2)
Yes	374 (5.4)	37 (11.2)	17 (14.8)
Number of antipsychotics used in the previous six months, mean ± SD (range)	1.0 ± 1.0 (0–8)	2.2 ± 1.2 (0–7)	1.2 ± 1.0 (0–6)
Previous clozapine use			
No	5643 (82.3)	151 (45.6)	80 (69.6)
Yes	1214 (17.7)	180 (54.4)	35 (30.4)
Previous LAI use			
No	4405 (64.2)	167 (50.5)	52 (45.2)
Yes	2452 (35.8)	164 (49.5)	63 (54.8)

[a] Antipsychotic polypharmacy (APP) lasting for six or more months.

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area) had an effect on the association between APP and all exposure variables. Patients resident outside the local catchment area can be referred to SLaM services for specialist treatment, due to particularly severe or treatment-resistant symptoms. Therefore, this group could be inherently different to local patients.

3. Results

We identified 7201 adults with a SMI diagnosis who were receiving SLaM care between January and June 2012. We excluded 344 patients as they were not receiving care in SLaM services in the six months prior to 1st January 2012, resulting in a total sample size of 6857 patients. We found that 331 (4.8%) patients were receiving antipsychotic polypharmacy for six or more months between 1st January and 30th June 2012 (this sample is also referred to as overall APP) and 115 (1.7%) were newly initiated on long-term APP. Table 1 summarises the characteristics for the total cohort and by overall and newly prescribed APP.

Table 2 describes the prevalence of first (FGA) and second-generation antipsychotics (SGA) that were prescribed as part of APP. Two or more SGAs were most commonly co-prescribed. Of the newly initiated sample, 24.3% were receiving clozapine APP.

Table 3 summarises results from the unadjusted and adjusted logistic regression models, which examine the potential socio-demographic and socioeconomic predictors of newly prescribed APP. In the fully adjusted model, individuals in early adulthood (aged 16–35) were more likely to be initiated on APP than older adults (aged 56+) (OR 2.1, 95% CI 1.1–3.7, $p = 0.016$), whereas being in a relationship was associated with a reduced risk for APP initiation (OR 0.3, 0.1–0.9, $p = 0.043$). Experiencing a high level of deprivation and more specifically being homeless was also associated with an increased risk for being newly initiated on long-term APP (OR 3.3, 1.1–9.9, $p = 0031$).

As described in Table 4, overall clinical symptoms, as measured by HoNOS administered closest to the start of follow-up, were not predictive of APP initiation, with the exception of significant problems with hallucinations and/or delusions (OR 1.6, 1.0–2.5, $p = 0.048$). In a sensitivity analysis, where the investigation was restricted to HoNOS scores obtained within the last year prior to the observation period, this association was not substantially changed in strength, although fell outside statistical significance (OR 1.5, 0.9–2.4, $p = 0.146$).

Table 5 summarises associations between newly prescribed APP and service use. We found that the risk of APP initiation increased with every additional day of outpatient contact (OR 1.0099, 1.0002–1.0197, $p = 0.045$) received in the previous six months, even after adjusting for possible confounders. Similarly, having previously received a CTO (OR 2.6, 1.5–4.5, $p < 0.001$), previous use of clozapine (OR 1.8, 1.2–2.7, $p = 0.006$), and previous LAI use (OR 2.2, 1.5–3.2, $p < 0.001$) were all associated with increased risk of being newly prescribed long-term APP in the fully adjusted models.

In total, 419 (6.7%) patients in the sample had been referred for SLAM services from other boroughs rather than being catchment area residents. A sensitivity analysis indicated that after restricting the analyses to patients residing in the SLaM catchment area, the magnitude and direction of ORs were similar for all associations; however some were no longer significant including being in a relationship ($p = 0.056$), having problems with hallucinations and/or delusions ($p = 0.123$) and outpatient contact in the previous 6 months ($p = 0.058$). Also, after excluding patients from outside the catchment there were no longer any homeless people prescribed long-term APP; therefore an analysis of this variable was not possible.

Table 2
Prevalence and distribution of long-term antipsychotic polypharmacy (APP).

Types of antipsychotic polypharmacy	APP (n = 331)		APP initiation (n = 115)	
	n	% (95% CI)	n	% (95% CI)
First generation antipsychotics (FGA) only	9	2.7 (1.3–5.1)	6	5.2 (1.9–11.0)
Second generation antipsychotics (SGA) only	216	65.3 (59.9–70.4)	62	53.9 (44.4–63.2)
FGA + SGA	106	32.0 (27.0–37.3)	47	40.9 (31.8–50.4)
APP inclusive of FGA or SGA LAI[a]	72	21.8 (17.3–26.2)	35	30.4 (21.9–38.9)
APP inclusive of clozapine[a]	165	49.9 (44.4–55.3)	28	24.3 (16.4–32.3)

[a] Categories overlap with APP by generation (FGA; SGA; FGA + SGA).

Table 3
Logistic regression analysis of socio-demographic and socioeconomic predictors of antipsychotic polypharmacy initiation.

	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted p-value
Age			
16–35	**2.6 (1.6–4.5)**	**2.1 (1.1–3.7)**	**0.016**
36–45	1.7 (0.9–3.0)	1.4 (0.8–2.6)	0.291
46–55	1.3 (0.7–2.4)	1.1 (0.6–2.1)	0.748
56+	Reference	Reference	
Gender			
Female	Reference	Reference	
Male	1.3 (0.9–1.9)	1.1 (0.7–1.7)	0.621
Ethnicity group			
White	Reference	Reference	
Black Caribbean	1.2 (0.7–2.2)	1.1 (0.6–2.1)	0.691
Black African	**1.8 (1.2–2.8)**	1.4 (0.9–2.3)	0.129
Other	1.3 (0.7–2.3)	1.3 (0.7–2.4)	0.403
Relationship status			
Not in a relationship	Reference	Reference	
In relationship	**0.3 (0.1–0.7)**	**0.3 (0.1–0.9)**	**0.043**
Employment status			
Not in paid employment	Reference	Reference	
In paid employment	0.3 (0.1–1.4)	0.4 (0.1–1.6)	0.181
Deprivation level			
Low level	Reference	Reference	
Medium level	1.6 (0.9–2.6)	1.4 (0.9–2.4)	0.164
High level	**1.7 (1.0–2.8)**	1.5 (0.9–2.5)	0.116
Homelessness	**4.7 (1.6–13.9)**	**3.3 (1.1–9.9)**	**0.031**

Values in bold are statistically significant (≤ 0.05).
[a] Models adjusted for all socio-demographic and socioeconomic factors.

4. Discussion

Our results indicate that age, socioeconomic circumstances, psychotic symptoms, prior outpatient contact, CTOs, prior clozapine and/or LAI use are significant, independent predictors of newly prescribed long-term APP.

Our findings are in keeping with existing research (Mace and Taylor, 2015) indicating that SLaM has a considerably lower prevalence of APP in comparison to a UK national sample and other US studies (Freudenreich and Goff, 2002; Gallego et al., 2012). Considering service use measures, our results both confirm previous research and generate novel findings. For example, our results support previous research which has indicated that prior service use, such as more frequent outpatient contact (Ganguly et al., 2004; Kreyenbuhl et al., 2007a, 2007b), previous use of LAI, and clozapine (Ganguly et al., 2004), are associated with an increased risk for longer term APP (i.e. >60 days). Importantly, our findings further indicate that only a third of the patients initiated on APP had previously been trialled on clozapine. This has been previously suggested (Howes et al., 2012; Nielsen et al., 2012), and highlights that prescribing guidelines (i.e. that APP should only be considered after trials of two individual agents followed by clozapine) are not consistently applied in 'real world' practice. Contrary to some previous reports, we found no evidence to suggest that APP initiation is predicted by the number of days spent as an inpatient or number of antipsychotics used (Barbui et al., 2006; Ganguly et al., 2004; Morrato et al., 2007) in the previous six months. An important issue to bear in mind is that

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Table 4
Logistic regression analysis of clinical predictors of antipsychotic polypharmacy initiation.

	Crude OR (95%CI)	Adjusted OR[a] (95% CI)	Adjusted p-value
Comorbid diagnosis			
Depression			
No	Reference	Reference	
Yes	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.286
Personality disorder			
No	Reference	Reference	
Yes	1.4 (0.9–2.3)	1.2 (0.7–2.0)	0.464
Substance use			
No	Reference	Reference	
Yes	1.2 (0.8–1.8)	1.0 (0.6–1.5)	0.873
Overactive and aggressive behaviour			
Not a problem	Reference	Reference	
Minor problem	1.3 (0.8–2.0)	1.3 (0.8–2.0)	0.331
Significant problem	1.3 (0.8–2.2)	1.3 (0.8–2.2)	0.339
Non-accidental self-injury			
Not a problem	Reference	Reference	
Minor problem	0.9 (0.4–2.2)	0.9 (0.4–2.2)	0.804
Significant problem	1.0 (0.3–3.1)	0.9 (0.3–3.0)	0.922
Cognitive problems			
Not a problem	Reference	Reference	
Minor problem	0.9 (0.5–1.4)	0.9 (0.6–1.5)	0.818
Significant problem	1.2 (0.7–2.0)	1.4 (0.8–2.3)	0.222
Physical illness or disability			
Not a problem	Reference	Reference	
Minor problem	1.1 (0.7–1.8)	1.4 (0.9–2.4)	0.159
Significant problem	1.1 (0.7–1.7)	1.6 (0.9–2.6)	0.064
Hallucinations and delusions			
Not a problem	Reference	Reference	
Minor problem	1.5 (0.9–2.5)	1.5 (0.9–2.5)	0.141
Significant problem	**1.7 (1.1–2.6)**	**1.6 (1.0–2.5)**	**0.048**
Problems with activities of daily living			
Not a problem	Reference	Reference	
Minor problem	1.2 (0.7–1.9)	1.2 (0.7–1.9)	0.506
Significant problem	1.2 (0.8–1.8)	1.2 (0.8–1.9)	0.414

Values in bold are statistically significant (≤ 0.05).
[a] Models adjusted for all socio-demographic and socioeconomic factors.

we specifically investigated APP initiation, while previous research has rarely been able to account for pre-existing APP use and thus has not been able to distinguish factors associated with its initiation from those associated with its continuation. Furthermore, it is important to consider service use predictors in the context of the service where they are examined. For example, in the UK, there has been a nationwide drive to reduce the number and duration of inpatient admissions. Therefore, it is possible that factors, which would have previously warranted an inpatient admission, are now possibly driving APP prescribing due to limited beds. Future studies may benefit from testing further whether APP is initiated in the community in order to prevent hospital admission. Our results further suggest that factors such as prior history of CTOs (a proposed proxy for non-adherence) are associated with an increased risk for long-term APP, something that has not been previously investigated (Biancosino et al., 2005; Patel et al., 2011).

Table 5
Logistic regression analysis of service use predictors of antipsychotic polypharmacy initiation.

	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted p-value
Days of inpatients stay in previous six months	**1.0 (1.00–1.01)**	1.0 (0.9–1.0)	0.309
Days of outpatient contact in previous six months	**1.0095 (1.0007–1.0183)**	**1.0099 (1.0002–1.0197)**	**0.045**
Number of antipsychotics used in the previous six months	**1.2 (1.0–1.4)**	1.1 (0.9–1.3)	0.291
Previous CTOs			
No	Reference	Reference	
Yes	**3.1 (1.8–5.2)**	**2.6 (1.5–4.5)**	**<0.001**
Previous clozapine use			
No	Reference	Reference	
Yes	**2.1 (1.4–3.1)**	**1.8 (1.2–2.7)**	**0.006**
Previous LAI use			
No	Reference	Reference	
Yes	**2.2 (1.5–3.2)**	**2.2 (1.5–3.2)**	**<0.001**

Values in bold are statistically significant (≤ 0.05).
[a] Models adjusted for all socio-demographic and socioeconomic factors.

Experiencing significant hallucinations and/or delusions, as rated on the respective HoNOS sub-scale, emerged as the sole symptomatic predictor of long-term APP initiation. This contrasts with some previous studies, where no associations were found between general psychopathology and long-term APP (Barbui et al., 2006); however, most studies of smaller inpatient samples (Biancosino et al., 2005; Centorrino et al., 2004, 2005) have indicated an association between APP and positive symptoms. Lastly, despite some previous evidence indicating that comorbid diagnoses such as personality disorder (Ganguly et al., 2004) and depression (Kreyenbuhl et al., 2007a, 2007b) are associated with reduced likelihood of APP prescribing, we detected no such associations with APP initiation.

Of the demographic factors that we examined, we found a positive association between APP and younger age (Kreyenbuhl et al., 2007a, 2007b; Morrato et al., 2007; Suokas et al., 2012). There are several potential explanations. For example, it is possible that younger patients are seen as better able to tolerate side-effects associated with APP (Alexopoulos et al., 2004; Shin et al., 2013) or that higher perceived risk (e.g. of violence) influences prescribing behaviour. Ethnic background and gender, in contrast to other studies (Ganguly et al., 2004; Kreyenbuhl et al., 2007a, 2007b; Suokas et al., 2012), were not significantly associated with APP. We found a potentially protective effect of being in a relationship (Kreyenbuhl et al., 2007a, 2007b), which could suggest that being able to sustain an intimate relationship may be seen as a marker for better functioning and less impairment. Deprivation level emerged as the sole socioeconomic factor that predicted initiating long-term APP. In contrast with previous research where the principal focus has been on employment status (Barbui et al., 2006), our study suggests that deprivation is potentially a more meaningful measure of socioeconomic status. It is possible that homelessness acts as a proxy for illness severity (Gaebel and Zielasek, 2015); however, this association is novel, and the role of socioeconomic features in general warrants further investigation.

This study had several strengths. Measuring predictors prior to APP initiation allowed us to separate the exposures and outcome, thereby reducing the influence of reverse causality. We also examined APP of at least six months duration, which is likely to have excluded cross-titration, although it is possible that some instances may have begun with this (i.e. where a cross-titration was commenced but not completed due to worsening symptoms, resulting in the observed APP). We explored multiple factors simultaneously as predictors and confounders, and used data from a large sample including both inpatients and outpatients. Finally, in common with most NHS Mental Health Trusts in the UK, SLaM is close to being a monopoly mental healthcare provider for its geographic catchment; therefore our sample is likely to be representative of patients seen by secondary care (Stewart et al., 2009).

There were several potential limitations. Despite adjusting for multiple confounders, it is possible that some residual confounding may have occurred. We were unable to measure factors such as duration of illness or stages of treatment as patients entered the observation period. In addition, we were unable to measure clinician related factors such as prescriber experience of initiating APP and knowledge of side-effects and adverse outcomes (Correll and Gallego, 2012; Correll et al., 2011; Gee et al., 2014). In contrast to previous research where standardised symptomatic assessments have been used (e.g. PANSS, BPRS), symptom assessment in this study was limited to individual HoNOS items,

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measured at one point in time. This scale has received some previous criticism with regards to its measurement of symptoms (Bebbington et al., 1999; Stein, 1999), and we were only able to analyse a composite measure of psychotic symptoms. It is possible that true associations may have been concealed, and further research is required into the role of observed and recorded symptomatology in clinical decision-making.

We believe that our findings have several important clinical implications. Long-term APP prescribing is unlikely to be predicted by a single factor, rather it is precipitated by a complex interplay between patient and wider environmental contexts, where clinical symptoms as well as service use such as previous treatment and contact with services may influence decision-making. Furthermore, our study highlights that there are certain patient groups, such as patients whose symptoms are resistant to treatment, that are at an increased risk for APP initiation. Although a proportion of patients prescribed APP do receive pharmacotherapy that is in line with current treatment guidelines (i.e. LAI and clozapine trials that precede APP initiation), a subgroup is offered APP sooner than recommended. Future research would benefit from focusing further on patients that are inappropriately initiated on APP, as a long-term treatment plan. Identifying these groups could encourage clinicians to employ a broader range of interventions, including earlier trials of clozapine and/or alternative treatments to pharmacotherapy to reduce the risk of APP prescribing.

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Contributors

GK, RDH, and RS designed the study. GK and HS extracted the data and conducted the analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

RDH, HS, and RS have received research funding from Roche, Pfizer, J&J and Lundbeck. DT has received research funding from BMS, Janssen and Lundbeck. DT is an Advisory Board member in Lundbeck, Servier and Sunovion.

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APPENDIX C

Appendix C was discussed on page 254 under ‘Additional analyses’ in Chapter 8. This table examines an alternative reference group for the analysis, where first episode of long-term polypharmacy was compared to a long-term monotherapy episode that occurred at or after the midpoint of the observation window (2010).

Supplementary Table: Sample characteristics of patients prescribed monotherapy and antipsychotic polypharmacy (n=9,085).

Variables	Monotherapy2010 n (%)	Antipsychotic polypharmacy n (%)
Total	6561 (72.22)	2,524(27.78)
Deaths	345	162
Socio-demographic and socioeconomic factors		
Age	41.28 (14.93)	38.07 (13.47)
Mean (SD)		
Gender		
Female	2,873 (43.79)	1,054 (41.76)
Male	3,688 (56.21)	1,470 (58.24)
Ethnicity group		
British	2,364 (36.03)	838 (33.20)
Other White	579 (8.82)	184 (7.29)
Asian	449 (6.84)	159 (6.30)
Caribbean	863 (13.15)	354 (14.03)
Black African	1,798 (27.40)	813 (32.21)
Other	508 (7.74)	176 (6.97)
Employment		
Not in paid employment	6,363 (96.98)	2,461 (97.50)
Paid employment	198 (3.02)	63 (2.50)
Relationship status		
No relationship	5,607 (85.46)	2,303 (91.24)
Relationship	954 (14.54)	221 (8.76)
Deprivation level		
Low level	2,132 (32.65)	805 (32.21)
Medium level	2,156 (33.02)	808 (32.33)
High level	2,143 (32.82)	821 (32.85)
Homelessness	98 (1.50)	65 (2.60)
Clinical factors		
ICD-10: F20	4,637 (70.68)	1,950 (77.26)
ICD-10: F25	492 (7.50)	235 (9.31)
ICD-10: F31	1,432 (21.83)	339 (13.43)
Comorbid Depression		
Yes	1,039(15.84)	301 (11.93)
Comorbid Personality Disorder		
Yes	751 (11.45)	379 (15.02)
Comorbid Substance Use		
Yes	827 (12.60)	272 (10.78)
Time known to SLAM		
Mean (SD)	1641.46 (1191.24)	2223.98 (1468.95)
Smoking		
Have smoked ever	4,720 (71.94)	2,150 (85.18)

APPENDIX D

Appendix D was discussed on page 254 under ‘Additional analyses’ in Chapter 8. This table examines an alternative reference group for the analysis, where first episode of long-term polypharmacy was compared to everyone else in the sample who did not qualify for the long-term antipsychotic polypharmacy group. This reference group included patients who were on long-term monotherapy and all other patients who were known to SLAM services for six or more months and that did not qualify for the polypharmacy group.

Supplementary Table: Sample characteristics of patients prescribed antipsychotic polypharmacy and those have not been prescribed polypharmacy. (n=16,871)

Variables	Everyone else n (%)	Antipsychotic polypharmacy n (%)
Number (%)	14,347	2,524
Deaths	1,434	162
Socio-demographic and socioeconomic factors		
Age Mean (SD)	42.25 (15.95)	38.07 (13.47)
Gender		
Female	6,738 (46.96)	1,054 (41.76)
Male	7,609 (53.04)	1,470 (58.24)
Ethnicity group		
British	5,979 (41.67)	838 (33.20)
Other White	1,491 (10.39)	184 (7.29)
Asian	850 (5.92)	159 (6.30)
Caribbean	1,536 (10.71)	354 (14.03)
Black African	3,138 (21.87)	813 (32.21)
Other	1,353 (9.43)	176 (6.97)
Employment		
Not in paid employment	13,820 (96.33)	2,461 (97.50)
Paid employment	527 (3.67)	63 (2.50)
Relationship status		
No relationship	12,170 (84.83)	2,303 (91.24)
Relationship	2,177 (15.17)	221 (8.76)
Deprivation level in area of residence		
Low level	4,639 (32.83)	805 (32.21)
Medium level	4,649 (32.90)	808 (32.33)
High level	4,587 (32.46)	821 (32.85)
Homelessness	257 (1.82)	65 (2.60)
Clinical factors		
Comorbid Depression		
Yes	1,894 (13.20)	301 (11.93)
Comorbid Personality Disorder		
Yes	1,140 (7.95)	379 (15.02)
Comorbid Substance Use		
Yes	1,217 (8.48)	272 (10.78)
Time known to SLAM		
Mean (SD)	1181.26 (1291.13)	2223.98 (1468.95)
Smoking		
Have smoked ever	7,240 (50.46)	2,150 (85.18)